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Therapeutic Symposium

FUNCTIONAL UTERINE BLEEDING

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FUNCTIONAL UTERINE BLEEDING may be defined as that which appears in the absence of gross lesions, at unexpected times, or in abnormal amounts. It is presumably due to dysfunction of one or more of the hormones, ovarian or pituitary, which are concerned in the menstrual cycle. The object of this symposium is to define this dysfunction and determine to what extent it accounts for the bleeding. Normal menstruation requires the activity of the pituitary and is under endocrine control. This applies to the usual cycle which is associated with ovulation, and to anovulatory cycles as well. A description of the normal cycle may be in order. The ripening of the ovum is accompanied by secretion from the follicle of estrogen, which causes proliferation of the endometrium and also prepares the vaginal wall for coitus. With ovulation the area of rupture closes and the cells take on the character of thecal cells to form the corpus luteum. These cells secrete progesterone which causes further growth of the endometrium and increased secretory activity in preparation for the fertilized ovum. When conception fails to occur the progestational endometrium breaks down, leaving only the basal layer. This is accompanied by the flow of nonclotting blood, i.e., menstruation.

Menstruation may be produced artificially in the castrated monkey or human being by the injection of ovarian hormones. Estrogen may be given over a number of days, and then replaced by progesterone. When the latter is withdrawn, bleeding occurs which has the characteristics of menstruation. A greater degree of hyperplasia is produced when the hormones overlap, as appears to be the case with the natural hormones.

The importance of uterine blood vessels in menstruation will be referred to by Dr. Kurzrok. Extensive studies have been reported by Markee and others. This author transplanted endometrium to the anterior chamber of the eye. The changes which he observed are reported by Bartelmez (1). "A blush and blanch" rhythm is observed which disappears gradually after castration. In monkeys before the onset of menstruation an ischemia is seen which lasts from 4 to 24 hours. This is accompanied or followed by a diminution in the size of the graft. Sooner or later an arteriole dilates here and there, and an extravasation of blood appears promptly about this. Lacunae of blood continue to appear for 36 hours. After 12 hours bits of tissue become detached. There is some evidence that this mechanism applies also to the human being. Histological studies in monkeys have shown that the ischemia is due to constriction of the spiral arteries. These studies suggest that insofar as the actual bleeding of normal menstruation is concerned the locus of endocrine control is in the spiral arteries. It appears logical to look here also for the explanation of pathological bleeding in the human being.

Bleeding occurs experimentally and clinically as the result of any procedure by which the supply of estrogen to the body is decreased (2). Thus it is observed after removal of the ovaries and occurs regularly with the interruption of estrogenic therapy. Diminution of the supply to a lower level suffices to produce bleeding. On the other hand, prolonged administra-

tion of estrin to castrated monkeys results in bleeding even while the administration is being continued. The bleeding which occurs experimentally from withdrawal of estrogen can be inhibited by the administration of progesterone, and this action is not prevented by the simultaneous administration of estrogens (2). When the administration of progesterone is discontinued bleeding takes place in the form of menstruation.

To what extent this mechanism applies to spontaneous bleeding in the human being is not clear. The opposite theory, i.e., excessive action of estrogen, is the one which is most frequently advocated. Attempts have been made to establish the etiology by means of histological studies of the endometrium. Most emphasis has been put on the hyperplastic endometrium, an exaggeration of the type which is observed normally with the ripening of the ovarian follicle. Such bleeding is associated with cysts of the ovary, and usually, but far from invariably, with the absence of corpora lutea. The inference is that because of the lack of ovulation the follicles secrete estrogen continuously instead of intermittently and that the endometrium thus becomes fixed in the hyperplastic stage. Bleeding, therefore, is thought to take place without the formation of a progestational endometrium and without the rapid desquamation of the latter, which is most characteristic of normal menstruation. It occurs, however, with any type of endometrium; atrophic, proliferative, hyperplastic, or progestational. In addition, irregular shedding and ripening has been described (3). The incidence of the hyperplastic type, according to Jeffcoate (4) does not exceed one-third of all the cases.

Classification of bleeding by hormonal assay has been attempted but the results are uncertain. More knowledge is needed concerning the chemical changes taking place in the metabolism of the sex sterols. Vaginal smears may be made but require long experience for interpretation in these patients.

Bleeding may occur with cyclic ovarian activity, whether the cycle is prolonged, short or normal. When it occurs twice a month the alternate bleedings are probably associated with the follicular stage of the ovary and are of no great clinical significance; the "Mittelschmerz" or "Kleine Regel" of the German writers. This phenomenon does, however, demonstrate the fact that bleeding can occur at the peak of estrogenic activity. Excessive bleeding at or following menstruation is known as menorrhagia, and non-cyclic bleeding as metrorrhagia.

Attempts to classify bleeding by means of age or menstrual history have not been widely accepted. In the case of hyperplastic endometrium it occurs most frequently with puberty and often with the menopause (4); that which is associated with a progestational endometrium comes nearly a decade earlier than the latter (5). Bleeding may take place, however, at any time during the childbearing age.

Functional uterine bleeding is very common. At best it is a social and marital disability, and at worst produces chronic anemia and not infrequently threatens life. The indications for treatment are to stop the bleeding, and if possible to prevent operations on the pelvic organs or radiation and the distressing effects which so often follow in their wake, as the etiology is little understood and the treatment is empirical.

The hormones may be discussed in the order of the frequency with which they have been used. The indications have been stated at length by Jeffcoate (4) and Hamblen (6). Anterior pituitary-like extract of pregnancy urine has been reported most extensively, with good results by most authors and no benefit by others. Some of the cases in each series fail to receive benefit. This was first employed on the theory that it would stimulate the formation of a corpus luteum and thus convert a bleeding hyperplastic endometrium into the progestational type which precedes normal menstruation. In the human being, however, the luteinizing effect of this extract is slight. Such extracts may produce local irritation and even a constitutional reaction with fever. These effects seem to have been more common with the earlier preparations than at present. If time permits it is advisable to give a preliminary dose of 0.2 cc. This may be followed on the second day with 250 rat units, to be repeated on the next day and three times a week. Kurzrok (see below) recommends large doses. Any standardized preparation from a reliable company may be used. Bleeding often ceases within a few days.

Androgens have been used more recently, but with a higher proportion of successes (7, 8). Testosterone inhibits experimental bleeding (9), suppresses menstruation in the monkey, also in the woman (10). It decreases the size of the ovaries and inhibits follicular activity. Thus it produces a temporary menopause. It may cause abnormal growth of hair, lowering of the pitch of the voice, and enlargement of the clitoris, but so far these effects have not been lasting, except for the persistence of slight excess of hair. There are numerous androgens which vary in their chemical constitution and in their effects, some of them approaching the estrogens. The dosage in terms of testosterone propionate is 25 to 50 mg. three times a week. Bleeding should stop in a few days.

The effect of estrogens has been little studied, as it is contrary to theoretical indications in cases with hyperplastic endometrium (4). It is said to be indicated only when the endometrium is atrophic. According to scattered reports, its use is followed by cessation of bleeding in some cases. The dosage may

be chosen as that which is effective in the menopausal syndrome, namely from 2,000 R. U. intramuscularly three times a week to 3,000 R. U. daily (10,000 I. U. or 1 mg. to 15,000 I. U. or 1.5 mg.) Either estradiol benzoate or estrone may be used.

The use of progestin has been suggested for several years but it has only recently become available on a large scale, and it is still very expensive. It inhibits experimental uterine bleeding in monkeys, and has been advocated on theoretical grounds in cases of hyperplastic endometrium. With the treatment bleeding should cease, to be followed after an interval of 3 to 5 days by a normal menstruation. The dosage is much less than the amount necessary to produce a progestational endometrium in a castrate woman. Five to 10 mg. of progesterone daily have been used.

From the preceding discussion it is evident that the hormonal treatment of bleeding is in the empirical stage both as to the selection of cases and the choice of preparation and dosage.

The choice lies at present between testosterone and anterior pituitary-like extract of pregnancy urine, with some advantage in the former. If one hormone fails another may be tried. The use of progesterone is theoretically sound in cases with a hyperplastic endometrium but is still in a tentative stage. Estrogens have a dramatic effect in a small group of cases, but these cannot be selected in advance. If effective, the bleeding stops in three or four days. The evaluation on empirical grounds of any form of therapy is precarious. This has been emphasized by Geist (11) who attributes all the reported beneficial effects of extract of pregnancy urine to coincidence. This again calls attention to the temporary nature of the bleeding and the necessity for conservative treatment.

By definition the type of bleeding under discussion is that in which no gross lesions can be demonstrated. The presence of certain lesions is not, however, a necessary contra-indication to hormonal therapy. The relation between fibromata and endometrial bleeding has been discussed by Blair (12).

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DISCUSSION

PATHOLOGICAL UTERINE BLEEDING IN EXPERIMENTAL ANIMALS

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The contributions of the experimental laboratory to the pathogenesis of uterine bleeding have been meager. The rhesus monkey has been used widely in attempts to explain the endocrine role in normal or experimental menstruation. A complete description of menstruation in the monkey or woman cannot yet be written but thousands of experimental menstrual and pseudomenstrual bleedings have been induced with hormonal agents. These induced episodes of uterine or menstruation-like bleeding must uniformly be considered normal, since instances of abnormal bleeding, either in duration or intensity, have rarely been induced. A condition vaguely approximating benign cystic and glandular hyperplasia of the endometrium has been induced in the monkey with endocrine agents (estrogens and

estrogen plus progesterone), but no pathological bleeding from such a deformed endometrium has been described. In fact, this reviewer has been unable to find any instance of any experimentally induced type of pathological uterine bleeding.

There is some tendency at the present to depart from the traditional definition of menstruation which became generally accepted following the work of Robert Schroeder. At that time it was stated that true menstruation was the periodic bleeding, with tissue loss, from a progestational or secretory endometrium. Schroeder and many other authorities at the present time consider that bleeding from any other type of endometrium than a secretory type is either a pseudomenstruation or is pathological in nature.

It is now clear, however, that periodic uterine bleeding, whether menstruation or pseudomenstruation, may be induced either in the monkey or in woman, following the withdrawal of any one of a number of hormonal agents. Such bleeding may occur from a proliferative or from a secretory type of endometrium, but usually cannot be distinguished from any natural cyclic menstruation either in frequency, intensity or duration. It is also now believed that anovulatory cycles are unfortunately not rare in women.

Without attempting a definition of normal menstruation, it is enough for present purposes to describe as pathological uterine bleeding, any uterine bleeding which departs significantly from that of the normal menstrual cycle in intensity or amount of the flow, and in the duration or length of the bleeding period. This eliminates from present consideration abnormalities of the menstrual cycle, which are in the main determined by time, with short or long menstrual cycles.

It was first demonstrated by Edgar Allen that uterine bleeding, which cannot be distinguished from normal menstruation, resulted from uni- or bilateral ovariectomy of an adult female monkey, or after the cessation of a course of injections of an estrogen.

Subsequently it was shown (Zuckerman, Corner, Hisaw) that a reduction in the daily dosage of the injected estrogen below the 'threshold' level, without complete withdrawal, also resulted in bleeding.

After the demonstration that progesterone, the hormone of the corpus luteum, would hold the estrogen-withdrawal bleeding in abeyance, but would permit such bleeding on withdrawal of the progestin, a distinction was made between the time interval, or latent period, between cessation of treatment and appearance of bleeding. In the case of estrogen withdrawal, the average interval between cessation of treatment and the first day of bleeding was 9.2 days, while the interval following cessation of progesterone injections was 2.9 days (with maximum range 2–4 days).

It has been demonstrated that testosterone propionate will maintain the proliferative endometrium of an estrogen treated monkey. On withdrawal of this androgen uterine bleeding occurs within the latency period characteristic of estrogen withdrawal i.e., 7 to 16 days (1).

A proliferative endometrium may be induced in a monkey by the use of testosterone propionate alone, without pre-treatment with an estrogen. The latent period before bleeding after cessation of this androgen alone is 15 to 25 days, and is longer than in those instances where androgen followed a pre-treatment with estrogen.

It has been shown that desoxycorticosterone acetate would substitute for progesterone in inducing a progestational endometrium in rabbits (2), and in ovariectomized and adrenalectomized cats (3). In ovariectomized monkeys desoxycorticosterone acetate will prevent the expected bleeding of estrogen withdrawal when given under the same conditions as progesterone (table 1).

TABLE 1. LATENT PERIOD OF BLEEDING AFTER HORMONE WITHDRAWAL. OVARIECTOMIZED MONKEYS PRE-TREATED WITH ESTROGEN, FOLLOWED BY DESOXYCORTICOSTERONE ACETATE.

Monkey No.	Daily dose DOCA	No. days treated	Uterine bleeding after last day of DOCA
	mg.		*days*
603	10	12	3
599	15	12	3
622	25	10	4
601	25	13	3
613	25	6[1]	4

[1] A lapse of four days after estrogen with no treatment, followed by 6 days of desoxycorticosterone acetate.

When the desoxycorticosterone acetate was withdrawn bleeding occurred on day 3, 3, 4, 3 and 4 respectively (table 1) after the last injection. The latent period for bleeding is similar to that of progesterone, but different from any estrogen or testosterone propionate.

In experimental monkeys a type of non-cyclic uterine bleeding has been reported by several investigators. Engle and Smith (4) observed that periods of bleeding would occur during the course of estrogenic treatment, even in animals in which the dose was periodically raised. This phenomenon has also been observed frequently in women who are under consistent and prolonged estrogenic therapy. Zuckerman (5) has observed one monkey which received daily treatment of 100 I. U. estrone for one year, and which had eight periods of bleeding during the course of treatment. It is to be noted that there were no lapses or variation in dosage during this period. Zuckerman has considered these phenomena in formulating an hypothesis of a varying endometrial threshold to estrogenic stimulation.

The uniformity of the intensity and duration of bleeding in the monkey after withdrawal of any of the hormones discussed is in remarkable contrast to the duration and intensity of the menstrual flow in woman. While no quantitative measure of the intensity of the menstrual flow has been made in monkeys, such blood loss is not profuse. The bleeding which follows deprivation of the hormonal agents used has not been excessive in character.

TABLE 2. DURATION OF BLEEDING IN OVARIECTOMIZED MONKEYS AFTER HORMONE WITHDRAWAL

Duration of bleeding in days	2	3	4	5	6	7	8	Total
Number of instances of bleeding	1	4	18	19	13	2	1	58

The duration of such menstrual-like bleeding is likewise not excessive, regardless of the dosage, length of treatment or identity of the hormone used, as shown by a representative series from our records. These include all the experimental bleedings of 12 monkeys, during December, January and February of last year, and are presented in table 2. The agents used were: α estradiol benzoate; the same followed by progesterone; estriol; ethinyl estradiol; α estradiol benzoate followed by pregneninolone and an estradiol benzoate followed by desoxycorticosterone acetate, and gonadotropic hormones. Yet with such diverse endocrine activators, the data for the duration of the bleedings fall into the range of normal expectancy.

A type of induced uterine hemorrhage in the immature rabbit has been reported by Zondek (6). Appropriate doses of human chorionic gonadotropic hormone for 5 days, causes uterine bleeding in some animals on day 6. The bleeding, unaccompanied by tissue loss, always occurs from a proliferative, never from a secretory endometrium.

Intravenous injections of estradiol cause a similar effect in the hypophysectomized or adrenalectomized animal as well as the normal rabbit (7).

Any relation between these phenomena in rabbits to the problem of menstruation or pathological uterine bleeding of primates is not at present apparent. It is known that pathological uterine bleeding in woman occurs from a wide range of endometrial conditions, from the atrophic to the hyperplastic.

While an experimental menorrhagia has not yet been produced by endocrine agents, some facts on the nature of normal menstruation have developed.

It may be a mistake to say that the withdrawal of one of the hormones "causes" menstruation; rather such a lack of hormone "permits" changes in the endometrium and its blood vessels, which result in the bleeding and the tissue fragmentation.

The details of the vascular phenomena are fully discussed by Bartlemez (8). Details of the structure of endometrial vessels have been described by Daron and by Okkels and Engle (9, 10, 11).

Further investigations may show relationships between hormone actions and structural changes in the endometrial vascular supply or in chemical or ionic changes in the endometrium during normal or pathological uterine bleeding. Until such facts are brought to light, therapy of these disturbing conditions must remain empirical.

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DISCUSSION

FUNCTIONAL UTERINE BLEEDING

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FUNCTIONAL BLEEDING may occur from any type of endometrium, cystic and hyperplastic, proliferative, progestational, or atrophic. Similarly, amenorrhea may be associated with the same types of endometrium. We have observed cystic glandular hyperplasia of the endometrium in cases of long standing amenorrhea. The gestational endometrium during pregnancy is not associated with bleeding except on very infrequent occasions. Another interesting type is that which begins at the time of ovulation, as ovu-

lation bleeding, but instead of stopping within a few days, continues actively up to menstruation. Throughout this type of bleeding the histological picture is that of the progestational phase commensurate with the advancing phase of the cycle. In spite of increasing progestational change in the histology of the endometrium as the cycle advances, the bleeding persists or may even become more active. The onset of menstruation is here denoted as a mere accentuation in the bleeding. We (1) have also noted the appearance of cystic glandular hyperplasia of the endometrium during the amenorrhea associated with lactation. The condition appears suddenly, lasts possibly two to four weeks and then changes to the proliferative or progestational type without intervening bleeding. Experimentally neither the pituitary nor the ovary is essential for bleeding. Clinically the ovaries are not essential for endometrial bleeding. We feel that the factors that are responsible for bleeding reside within the endometrium proper, and whether bleeding will occur or not, depends on these factors and not upon the histological type of endometrium. In our opinion (2) the factors are essentially vascular. Much of the bleeding in cystic hyperplasia of the endometrium may be due to the severe congestion of the blood vessels resulting in their mechanical rupture, and extravasation of blood into the stroma with desquamation of fragments of endometrium.

The etiological factors of functional bleeding are obscure. The usual explanation of estrogen withdrawal describes an event, applicable in some cases only, and nothing more. This does not explain the bleeding that is clinically noted during continuous injections of large doses of estrogen. Several episodes of bleeding may occur at regularly stated intervals (four weeks or so) without the injections being stopped or diminished in amount. Estrogen withdrawal does not seem applicable here.

Functional bleeding has usually been associated with cystic glandular hyperplasia of the endometrium. The etiology of such hyperplasia is still a mooted question. The usual explanation has been that of excessive estrogen supply, the source of this estrogen being in either one or more large follicular cysts, or in numerous small cystic follicles. What evidence is there of such excessive estrogen production? Neither the blood nor the urine show larger estrogen titers, in fact, they just as frequently show lower figures than normal. Nor do the other tissues supplied by estrogen show the effects of overstimulation, such as hypertrophy or (and) engorgement of the uterus or the breasts. On the contrary, one frequently finds a hypoplastic uterus and (or) breasts in association with cystic glandular hyperplasia of the endometrium. It is this latter association that makes us doubt the entire theory of excessive estrogen production as the sole etiological factor of cystic and glandular hyperplasia of the endometrium. In a previous paper (3) we proposed the idea that many functional disturbances are due to abnormalities in the distribution of a normal hormone supply. That is, a given tissue (such as the endometrium, myometrium, breast, etc.) may take out of circulation more (or less) than its allotted share of hormone, and thereby undergo functional and anatomic disturbances leading to definite clinical syndromes. We believe that cystic glandular hyperplasia of the endometrium is due to an inherent disturbance in estrogen metabolism within the endometrium, with the result that the endometrium takes more estrogen out of circulation than is necessary for its normal function. Whether the other tissues suffer from this estrogen deprivation depends upon the amount withdrawn. As the result of this estrogen withdrawal by the endometrium the available supply of estrogen falls, and the ovary responds by producing more estrogen. It does so by the production of numerous follicles. (These remain as follicles, for the formation of corpora lutea from such follicles would lessen the hormone supply.) Hence, the cystic follicles noted with cystic glandular hyperplasia of the endometrium are the result of the hyperplasia and not the cause of it. This is borne out clinically in many cases wherein no demonstrable ovarian enlargement is noted at the onset of the syndrome, but only after it has progressed for some time. The production of cystic follicles is probably mediated by the way of the pituitary gland.

Bleeding may or may not be associated with cystic glandular hyperplasia. When it occurs it may, as previously stated, be due to such marked thickening and engorgement that the endometrium breaks down. On the contrary, we offer the suggestion that the bleeding may be, at least in the beginning of the syndrome, a protective mechanism. For how may the condition right itself? As the syndrome progresses the endometrium keeps growing. The more it grows, the more hormone it requires and, as a result of this, more hormone is produced by additional follicles brought up to meet this demand. The greater the supply of hormone, the greater becomes the endometrial growth; a vicious circle is thereby produced. The circle could be broken by diminishing the amount of functioning endometrium. The organism does that by the production of hemorrhage into the stroma, which in turn causes large fragments of endometrium to be desquamated. Much less hormone is now required, less is produced by the follicles, the production of follicles ceases and the condition adjusts itself. The treatment suggested by Hamblen (4) and Jeffcoate (5) utilizing large doses of estrogen (and progesterone) may have must such a desquamating effect.

It is a clinical fact that curettage is occasionally beneficial in cases of cystic glandular hyperplasia. The bleeding ceases, the cystic ovaries then regress and the patient returns to regular cycles. We believe that the curettage removes a large quantity of abnormally functioning endometrium. Bleeding temporarily ceases. If the newly regenerated endometrium has a normal estrogen metabolism, the cystic ovarian follicles regress and the patient returns to normal. If the newly regenerated endometrium retains its abnormal estrogen metabolism, the follicles persist and the bleeding is resumed. This explains why only few cases of functional bleeding are completely improved by curettage.

The beneficial effect of androgens in functional bleeding is now well known. They produce an inhibition of ovulation, and menstruation and atrophy of the endometrium (6–9). Whether the action of the androgen is by way of the pituitary (10) or by a direct effect on the metabolism of the estrogens by the endometrium is not as yet known. But again we break into the vicious cycle by the removal of the endometrium, here through atrophy.

The inhibiting effect of pregnancy urine gonadatropins on functional bleeding has not been satisfactorily explained. Cases of cystic glandular hyperplasia of the endometrium treated with P U gonadatropins present the following.

a) The ovaries fail to show the formation of corpora lutea. The cystic follicles persist (11). Hence the beneficial effect is not through the production of progesterone.

b) After the bleeding has ceased the endometrium remains in a state of cystic glandular hyperplasia for as long as six or more months (2).

c) The beneficial effect of P U is not in proportion to the number of rat units in the preparation. In fact, we are of opinion that the substances that inhibit the bleeding are other than prolan A and B, and as such are either lost or destroyed in the process of purification (12). The older preparations, containing 100 R.U. per cc. were far more efficacious therapeutically than the present preparations containing 1000 R.U. per cc.

What, therefore, is the modus operandi of P U gonadotropin in this syndrome? It may alter the estrogen metabolism of the endometrium, possibly in an inhibitory manner. Then again, it may inhibit those vascular factors which actually produce the bleeding. It might be mentioned in this connection that P U gonadotropin favors the metabolism of progesterone as evidenced by an increased excretion of pregnandiol glucuronide. The action of P U gonadotropin during pregnancy is still unexplained. Its function may be to alter the metabolism of estrogen by the endometrium (decidua) to such an extent as to prevent its utilization of the large amounts of available estrogen. Bleeding during pregnancy would thus be inhibited.

We use the following therapeutic measures.

a) Where the bleeding is profuse or if the hemoglobin is less than 50%, the patient is put to bed. The usual medical measures such as iron, liver extract, and diet are instituted.

b) When the hemoglobin is less than 40% the patient is transfused with 300 to 500 cc. of blood. The donor is a pregnant woman. We formerly chose only patients in the middle trimester of pregnancy, the reason being that the concentration of P U gonadotropin is greatest during the early part of this period. We have recently chosen donors in the other trimesters of pregnancy with equally good results. The bleeding usually ceases within 48 hours. It is frequently curative. A period of amenorrhea lasting several months may then follow or normal cycles may occur. We have found it necessary to retransfuse only once. Placental blood could be used but we have had no experience with it.

c) Testosterone propionate[1] is injected. The dose is 25 mg. daily until the bleeding ceases. The total dose never exceeds 250 mg. All injections are given intramuscularly in the buttocks. We do not apply this therapy to patients showing androgenic symptoms, (hirsutism, hypertrophy of the clitoris, homosexuality). We believe that the total dose of 250 mg. will not produce androgenic symptoms in previously normal women. When slight hirsutism does appear it has always regressed rapidly upon the conclusion of treatment. Small doses of androgens (10 mg. or less) given over short periods of time have not proved effective in our hands. If the bleeding does not cease within one week of the last dose another form of therapy is resorted to.

d) Pregnancy urine gonadotropins are not applied as frequently as before, for reasons which we stated above. When P U is used the dose ranged from 1000 to 2000 R.U. daily. This therapy is continued for a maximum two weeks. When successful, the therapy is frequently followed by a long period of amenorrhea.

e) The combined use of estrogens and progesterone may be attempted. We have injected 200,000 I.U. of estradiol benzoate in 4 divided doses during 10 days, followed by 40 to 50 mg. of progesterone during the following week. A marked increase in the bleeding may occur, associated with the passage of large fragments of endometrium. This is usually followed by a cessation of bleeding and a resumption of normal cycles.

f) Patients close to menopause are best treated by a diagnostic curettage followed by a sterilizing dose of x-ray or radium. We have found that patients close to

[1] Perandren, Ciba; oreton, Schering.

menopause are often not very responsive to the hormonal therapy outlined above.

g) Curettage as a sole method of therapy is rarely used.

h) We have found ergot preparations or posterior pituitary extracts to be without therapeutic value in these cases.

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DISCUSSION

GYNECOLOGICAL AND PATHOLOGICAL ASPECTS OF FUNCTIONAL UTERINE BLEEDING

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If the term "functional uterine bleeding" is used to include any abnormal hemorrhage "in the absence of gross lesions," it is found that many different factors are involved and not merely a single clinical or pathologic entity. There is no completely satisfactory classification of the various causes, but an approach may be made by considering the clinical manifestation of the bleeding and the histologic appearance of the endometrium.

A complete history of the abnormal bleeding and its relation to the normal menstrual cycle is of primary importance, but unfortunately it is not always available. These patients should be encouraged to keep a careful record on a calendar. A specimen of the endometrium should be obtained for histologic study, either by an extensive currettage under anesthesia or by means of a biopsy with one of the suction curettes developed in recent years (1, 2). It is important that this examination be made early during a bleeding episode and not during an interval, since the appearance of the uterine mucosa may vary greatly under the two conditions.

On the basis of the clinical history and the examination of the endometrium, functional uterine bleeding may be classified as follows.

A. CYCLIC BLEEDING ASSOCIATED WITH OVULATORY MENSTRUAL CYCLES
   a) Menorrhagia
   b) Polymenorrhea
   c) Cyclic interval hemorrhage

B. CYCLIC BLEEDING NOT ASSOCIATED WITH OVULATORY MENSTRUAL CYCLES
   Metropathia hemorrhagica

C. ARRHYTHMIC UTERINE HEMORRHAGE
   a) Atypical irregular hemorrhage
   b) Continuous bleeding starting at the time of an expected menstrual period
   c) Interval hemorrhage
   d) Bleeding after a period of amenorrhea

A. Cyclic Bleeding Associated with Ovulatory Menstrual Cycles

a. Menorrhagia. The terms menorrhagia and hypermenorrhea are applied to the occurrence of a succession of unduly profuse or prolonged menstrual periods. In these cases ovulation occurs so that neither the ovaries nor the endometrium show any deviation from the normal. A flow of more than seven days' duration should be considered as pathologic, and may be found with cycles of average length as well as with polymenorrhea.

It is probable that endocrine disorders may be etiologic factors, but it is difficult to determine the exact mechanism by which profuse menses are produced. Theoretically, an excessive activity of ovarian function resulting in overgrowth of the endometrium prior to menstruation may result in excessive bleeding, and the fact that a marked increase in the estrogen content of the blood occurs in some cases of menorrhagia supports this concept (3). Menorrhagia also is seen in some instances of hypothyroidism, but in the vast majority of cases it is observed in women with organic pelvic diseases or systemic conditions such as the various blood dyscrasias.

b) Polymenorrhea. The menstrual cycles of normal individuals are subject to considerable variation in

length, but at times there is such a marked shortening of consecutive cycles that attention is directed to them as evidence of some disorder. In polymenorrhea the usual course of events goes on both in ovaries and endometrium so that there are no characteristic pathologic changes, but the cycles last only 14 to 25, instead of the average 30, days.

It is often stated that this abnormality is brought about by a hyperhormonal condition, that is, by an overactivity of the ovaries. This contention is open to question, and on the basis of Schröder's studies it is more likely that it results from an ovarian deficiency which manifests itself by a premature disintegration of the corpus luteum, this leading to a shortening of the post-ovulatory phase of the cycle (4).

Although it is the least common type of menstrual irregularity, and is found in women who are normal in all other ways, polymenorrhea is an important symptom pointing to a pathologic condition. It is found frequently in the preclimacterium, in ovarian deficiencies associated with hypothyroidism, and it may have a psychogenic origin and result from fear of pregnancy or infection, and various sexual perversions. Most often it accompanies organic pelvic disease, chiefly pelvic inflammations, fibromyoma uteri and, rarely, uterine retrodisplacements. In such cases the shortened cycles must be attributed to vascular disturbances which directly affect the ovaries.

c) Cyclic interval hemorrhage is uterine bleeding which occurs cyclically from an endometrim with the characteristics of the normal late proliferative or early secretory stage. It appears at about the time of ovulation, that is, from 10 to 20 days before the onset of menstruation (5). It long has been recognized and given the names of "ovulation bleeding," "false menstruation," "little menstruation," or "supernumerary menses."

It may occur at any time between the menarche and the climacterium, but may spontaneously disappear after a few times. In some cases the amount of blood loss is equivalent to that of a menstrual period, but most often there is only a very scant flow. It is frequently associated with pelvic pain which sets in at the middle of the cycle (*Mittelschmerz*). The cause of the condition is not known, but it is comparable to the proestrous bleeding of dogs (6).

B. Cyclic Bleeding not Associated with Ovulatory Menstrual Cycles

Metropathia hemorrhagica. This term was applied by Schröder to a characteristic ovario-uterine disturbance which also has been named hyperplasia of the endometrium, endometritis ovarialis, hemorrhagic endometritis, functional or idiopathic uterine bleeding. It is of primary importance because it accounts for approximately half of all instances of uterine hemorrhage in the absence of gross pelvic lesions.

Since one-third of these patients have periods of bleeding at cyclic intervals (7), it is described under the above heading. From a clinical point of view this observation is important because the disease may be confused with menorrhagia or polymenorrhea. However, it must be remembered that in the remaining two-thirds the bleeding occurs continuously or at irregular frequent intervals. At times it appears following a period of amenorrhea and so may be confused with incomplete or threatened abortion.

This disease is found at all ages but is especially prone to occur shortly after the menarche and in the preclimacteric period. Although it is a definite endocrine entity, there are no particularly characteristic general features, but a careful pelvic examination frequently reveals a pelvic hyperemia and a moderate enlargement and softening of the uterus.

In metropathia hemorrhagica the ovaries may be slightly enlarged and contain from a few to many cysts representing various stages of follicular atresia, the most characteristic feature being an absence of corpora lutea. There is thus a failure of ovulation in these patients, so that the endometrium is constantly stimulated by estrogenic hormones in the absence of the progestin influence. The same result is obtained in the presence of granulosa-cell tumors of the ovary, and is of special interest when it appears during infancy and in the post-climacterium.

The uterine mucosa reflects this abnormal stimulation from the ovary. It is usually thickened and edematous, and the surface has irregular prominences. Histologically, the normal cyclic changes are lacking, and it presents the abnormal development known as "hyperplasia of the endometrium." The stroma is dense and cellular, the cells are spindleshaped, and there are large blood vessels coursing through the tissues from the basal layer to the surface. The glands show evidence of overgrowth, they are very numerous, arranged in a disorderly fashion, and there is a great variation in their size and shape. A characteristic finding is that of large cystic glands scattered throughout the mucosa. If the specimen is obtained at a time the patient is bleeding, thrombosed blood vessels with local areas of necrosis may be observed, and there is an extensive infiltration with leucocytes (8, 9, 7).

C. Arrhythmic Uterine Hemorrhage

a) Atypical irregular bleeding. The occurrence of arrhythmic uterine bleeding having no relation to menstruation is a frequent event and in the vast majority of instances it is attributable to organic lesions of the pelvic organs such as newgrowths or inflammation. In a smaller group, however, there is no demonstrable pathologic change, and the cause of the

bleeding remains a mystery. These cases must be classed as "functional bleeding" for lack of more complete understanding. The clinical and pathologic findings in this group are partly responsible for the statement that functional uterine bleeding may occur from an endometrium representing all phases of activity or inactivity.

b) Continuous bleeding starting at the time of an expected menstrual period. In this division is included prolonged uterine bleeding in women whose menses previously have been normal. It is characterized by the fact that the hemorrhage sets in at the expected time of menstruation, and continues for days or weeks or even as long as two and three months.

This clinical picture is generally due to local lesions which interfere with the proper healing of the endometrium following desquamation of the superficial layers. The cause usually is an endometrial polypus or inflammation due to gonorrhea or septic abortion. An interesting abnormality found in these patients was first described by Pankow (10), and may be termed "prolonged defective desquamation" or "irregular shedding of the endometrium" (11). Histologically it represents an imperfect desquamation of the surface of the mucosa with incomplete attempts at regeneration. The cause is not known, and although it has been suggested that the basic disturbance is of endocrine origin it may just as well result from a local endometrial deficiency. In support of this concept is the fact that a complete cure generally follows a thorough currettage.

c) Interval hemorrhage. In the section devoted to periodic uterine bleeding attention was directed to so-called ovulation bleeding. A similar, but not recurrent, clinical picture is seen where a sudden injury occurs to a mature follicle or developing corpus luteum during the intermenstruum, leading to atresia of the ovarian structure and a "premature menstruation." This condition has been noted by many observers following gross lesions such as the twisting of the pedicle of an ovarian cyst, torsion of the fallopian tube, and gross rupture of a corpus luteum with intra-abdominal hemorrhage. It also may be found in women with acute salpingitis and serves as evidence pointing to an intra-ovarian extension of the inflammatory process (12).

The uterine hemorrhage in such cases must be considered as of physiologico-pathologic origin, but gross lesions are demonstrable in the pelvis. In this sense they are not open for discussion in this forum, but nevertheless this type of bleeding may be found in patients with no demonstrable pelvic disease and must definitely be considered as "functional" in nature. This condition has been described for some years but has been almost completely overlooked in American medical literature.

The clinical picture is typical (13, 14). The patient gives a history of previously normal menses, and is seen because of a bodily injury occurring during the mid-interval. The accident may be a fall, a blow, and, in these days, generally an automobile crack-up. Investigation of the pelvis fails to reveal any positive findings except possibly some tenderness on one side or the other. The complaint is of uterine bleeding which begins a short time after the accident and lasts for a few days. The diagnosis is clinched by a delay of from two to three weeks in the appearance of the subsequent menstruation.

d) Bleeding after a period of amenorrhea. This type of uterine hemorrhage suggests the existence of an accident of gestation, or an ulcerative lesion in women past the climacteric or with post-castration amenorrhea (15). It must be kept in mind, however, in any consideration of 'functional uterine bleeding' because it is so often (18%) found in metropathia hemorrhagica. In such instances a correct diagnosis is dependent on the employment of the Aschheim-Zondek or Friedman test, and the proper interpretation of an endometrial biopsy.

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SUMMARY

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A CONSIDERABLE degree of unanimity is expressed in the foregoing papers, considering that they were written independently. A distinction must be made in the degree to which normal menstruation is understood, in contrast to functional uterine bleeding. The normal process is under endocrine control, and the events are clear in relation to the secretion of hormones and the cyclic changes in ovary, endometrium and blood vessels. By contrast, pathological bleeding can be understood only partially, and therapeutic control by endocrine means is far from complete. Experimental evidence does not help as much as might be expected. Dr. Engle has pointed out that the bleeding is not pathological either in intensity or duration. Factors in addition to the above must therefore be sought to explain the bleeding. Dr. Kurzrok emphasizes the possible role of the blood vessels, and puts forward an attractive theory, that there is a variation in the extent to which a tissue takes up hormones from the circulating blood. Dr. Fluhmann emphasizes the more external factors: infection, trauma, constitutional disease, and the presence of gross lesions such as fibromyomata. He mentions alterations in blood vessels in connection with some of these. Whether these influences operate directly or through hormonal mechanism, remains for the future to decide.

The recommendations as to the type of endocrine treatment are in substantial agreement. Dr. Kurzrok has contributed observations on the transfusion by a pregnant donor. Dr. Kurzrok, in common with many gynecologists, recommends radiation in patients approaching the menopause. In an endocrine clinic the the author of this summary has seen so much distress as the result of an artificial menopause, even at this age, that he is reluctant to advise this procedure except as a last resort. It may be that in such a clinic one sees a concentration of ill effects, but at all events a more certain control of the bleeding by hormones is highly desirable. This in turn requires a better understanding of the causes of functional uterine bleeding. It is hoped that this symposium will clarify the problem, and indicate the direction for further research.

VASCULAR HYPERTENSION IN PREGNANCY

URINARY EXCRETION OF PREGNANDIOL GLUCURONIDATE IN THE HYPERTENSIVE DISORDERS OF PREGNANCY*

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IT HAS BEEN SHOWN that pregnant women suffering from eclampsism, the acute hypertensive toxemia of pregnancy, excrete abnormally small amounts of pregnandiol glucuronidate in the urine (1–6). No study has yet been made, however, of excretion in pregnant women afflicted with chronic hypertensive disease.[1] Although the latter disease is obviously not confined to the gestational period, it accounts for a majority of the abnormal elevations of blood pressure encountered therein (7). We have accordingly examined the output of pregnandiol glucuronidate in a group of chronically hypertensive pregnant women, as well as in a group exhibiting typical eclampsism. Particular attention has been directed to the time in gestation at which abnormalities of excretion are first encountered, since previous studies of toxemic patients have thrown little light on this. Our purpose has been to determine whether abnormalities of excretion in toxemic women can be correlated with any of the clinical phenomena exhibited by such women.

METHODS

The methods of collection, preservation and work-up of the 24-hour volumes of urine used in this investigation were the same as those reported by us for a study of pregnandiol excretion in normal pregnancy (8). They were essentially those devised by Venning (9).

In view of the low values obtained by previous workers for pregnandiol glucuronidate output in toxemia of pregnancy, and because proteinuria is a characteristic feature of this disorder, it seemed desirable to determine whether the presence of protein interferes with the recovery of this compound from urine. For this purpose several experiments were made in which the yields of glucuronidate obtained from specimens of pooled urine of normal pregnancy were compared with those of equal specimens containing added blood serum (2 to 5 volumes per cent). In other experiments pure sodium pregnandiol glucuronidate (10 to 15 mg.) was added to specimens of albuminous male urine, and to albuminous pregnancy urine possessing a known content of preformed glucuronidate. In no experiments were the yields or recoveries of glucuronidate less complete from albuminous than from normal urine, nor were significant differences noted in the purities, as judged by melting point data, of the products obtained from each type of urine.

In conformity with previous reports, our recoveries of pregnandiol glucuronidate have been recorded in terms of free pregnandiol. They have been plotted upon charts, each of which summarizes the results obtained in an individual patient. Each chart has been provided with a background showing the normal ranges of pregnandiol excretion for the period of pregnancy represented. The data for normal gestation, obtained in the study previously referred to (8), have been illustrated in a more complete form in figure 1. The results of the latter study confirmed the original data of Venning (9).

The terms employed in classifying the various

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[1] By the term 'chronic hypertensive disease' we mean the disorders variously diagnosed as essential hypertension, benign nephrosclerosis, malignant hypertension, malignant nephrosclerosis, etc. The inclusive term is employed because there appears to be no general agreement among either pathologists or clinicians concerning the morbid anatomy and nomenclature of these disorders.

hypertensive disorders are those recommended by a sub-committee of the American Committee on Maternal Health (7). Five principal varieties of hypertension are specified in this nomenclature: eclampsia, severe pre-eclampsia, mild pre-eclampsia, chronic hypertensive disease, and nephritis. Most obstetricians regard the first three of these disorders as being different phases of a single disease or disease-syndrome, known as eclampsism. Nephritis is rarely seen among parturient women, and the patient material of this investigation includes no example of it. The criteria used in identifying the various disorders are revealed in our case protocols.

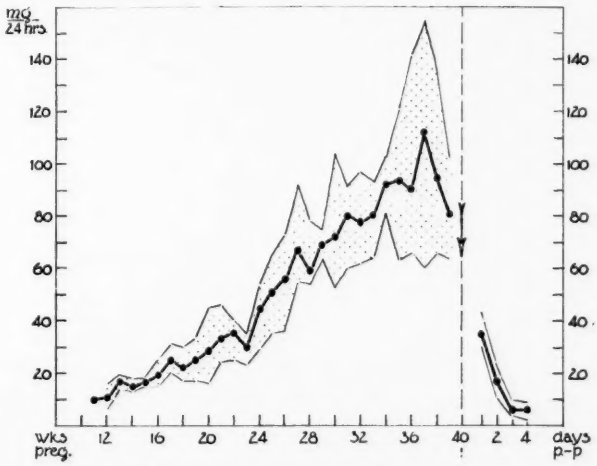


Fig. 1. PREGNANDIOL EXCRETION DURING PREGNANCY IN SIX NORMAL WOMEN. Abscissa represents menstrual age of pregnancy in weeks, and post-partum period in days. Ordinate shows urinary excretion of pregnandiol, mg./24 hr. Heavy dotted line shows curve of mean daily excretion for each week of gestation, and for first 4 post-partum days. Stippled area represents extreme deviations of the means.

Note: *a*) Progressive increase of excretion during gestation; *b*) Cyclic monthly fluctuation in curve of mean excretion; *c*) Pre-labor drop; *d*) Narrow range of deviation from mean excretion at all periods of pregnancy except during last month; *e*) Lowermost level of normal excretion rarely less than 60 mg. during last 8 weeks of gestation; *f*) Rapid disappearance after delivery.

RESULTS

Pre-eclampsia. Three primigravidas exhibiting this syndrome were studied, of whom 2 showed the mild, and 1 the severe form. Since the clinical and experimental findings of the 3 patients were analogous, the data of 1 patient only have been selected for purposes of illustration (fig. 2). The examinations of the urinary excretions of this patient were begun early in pregnancy, and were continued to include the first 5 days of the puerperium.

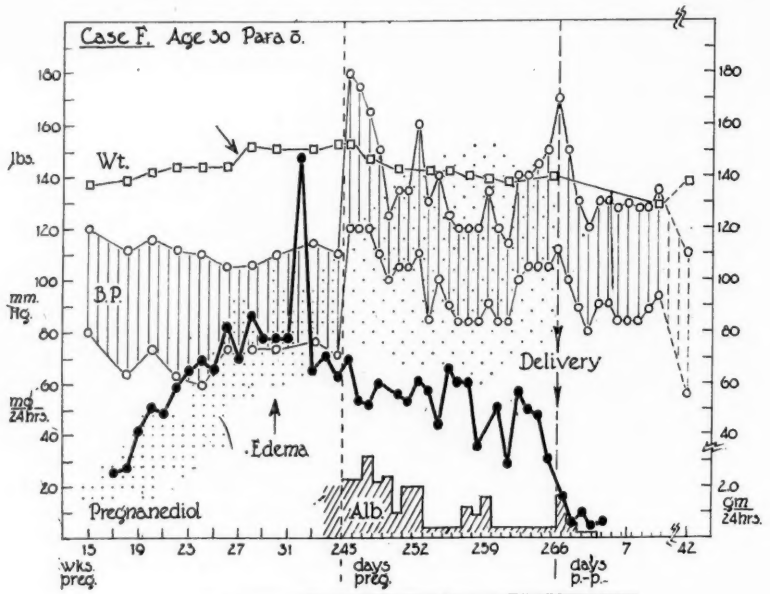
Maternal health and pregnandiol glucuronidate excretion were both normal until the 31st week of gestation. At that time the patient developed pretibial edema and shortly thereafter, a transient abnormal rise in the output of glucuronidate. At the 35th week her blood pressure rose sharply and a marked proteinuria appeared; at this point the excretion of the glucuronidate dropped to a level which was approximately one-half of normal. During the subsequent 3 weeks the patient's clinical condition improved under treatment, but excretion of the glucuronidate continued at a low level. At the end of this period, that is, at the 38th week, she fell into labor and gave birth to a premature living infant. After this, the compound disappeared from the urinary excretions with normal rapidity.

Mild chronic hypertensive disease. Three patients were studied, aged 23, 27, and 36 years respectively, in whom moderate elevations of blood pressure had been noted either before the beginning of pregnancy, or before the 20th week of gestation. Two of the patients were multigravidas. From none of them could a history of antecedent nephritis be elicited, nor of toxemia in antecedent pregnancy. Studies of renal function, carried out early in the course of the current pregnancies, showed no abnormalities; these investigations included examinations of renal concentrating function (Mosenthal test), of urinary sedi-

ments (Addis method), of urea clearances and of blood urea nitrogen levels. The retinal arteries showed angiospasm but no sclerosis. Blood pressure responses to cold pressor tests (10) were moderately exaggerated.

As gestation advanced in each case, the blood pressure showed the fluctuations typical of mild hypertension, but did not tend to rise appreciably above pre-pregnancy maxima of 150 mm. Hg systolic, and 100 mm. diastolic. In no patient did either edema or proteinuria develop. Except for the fact that labor occurred prematurely in 2 instances, the clinical courses of the pregnancies were essentially normal. Illustrative data from one of the patients have been recorded in figure 3. The excretion of pregnandiol glucuronidate in this patient, as in the others, was within normal limits.

Severe chronic hypertensive disease. Four patients were observed in whom marked and 'fixed' elevations of blood pressure were either known or presumed to have been present for several years. Three of the patients were primigravidas aged 18, 27 and 27 years respectively, and one was a multigravida aged 38. In the latter patient the retinal vessels were sclerotic. Otherwise, the histories of these patients and the studies of their renal function were as devoid of significant findings as were those of the moderately hypertensive patients discussed above.



Edema	+++	+	0	0	0
Ser. Prot.	5.2	6.0		5.8	
B.U.N.	10	13	13	15	9
Ur. Conc.	31	–	–	–	27
Ur. Clear.	90	–	–	–	94

Fig. 2. PREGNANDIOL EXCRETION IN PRIMIGRAVIDA SUFFERING FROM PRE-ECLAMPSIA. Abscissa represents duration of pregnancy and post-partum period. Observations at weekly intervals from 15th to 35th week; at daily intervals thereafter, and one observation on the 42nd day post-partum. Ordinate records body weight (Wt.) in lb.; blood pressure (B.P.) in mm. of Hg; pregnandiol excretion in mg./24 hours; and gm. of albumin (Alb.) in urine per 24 hours. Stippled area represents range of pregnandiol excretion for normal pregnancy.

Listed beneath the chart are data, obtained on 5 occasions corresponding to the days indicated in the chart itself, for the following: Serum protein (Ser. Prot.) in gm.%; specific gravity of urine (Ur. Conc., 31 = 1.031) following a Mosenthal concentration test; and urea clearance (Ur. clear.) in per cent of normal function.

Note fall in pregnandiol excretion coinciding with onset of albuminuria and hypertension.

The course of gestation was similar in all 4 patients. The facts concerning 2 of them are illustrated in figures 4 and 5. Proteinuria developed prior to the 28th week in all of the patients and, despite the fact that the patients were confined to bed thereafter, increased as pregnancy advanced. The blood pressures of 2 patients rose gradually above preceding levels during this proteinuric period. Edema and symptoms of eclampsism or hypertensive encephalopathy did not appear at any time in any of the

patients, nor did they exhibit significant depressions of renal function. Eventually, however, abnormal numbers of cells appeared in the urinary sediments, associated with a continuing rise in the concentration of urinary protein which made it advisable to terminate gestation. Although this was usually postponed until it was felt that the fetuses were viable, the latter were underdeveloped at birth with reference to normal criteria for body length and weight at their respective gestational ages (11, 12). The excretion of pregnandiol glucuronidate in all the patients fell to abnormally low levels as soon as proteinuria developed, and remained low until gestation was terminated.

DISCUSSION

The records of pregnandiol glucuronidate excretion obtained in this study include data pertaining to the principal varieties of vascular hypertension seen in parturient women except those associated with nephritis. Abnormally low levels of excretion were found only when proteinuria was present. This was the case not only where the hypertension had developed acutely during the course of gestation, as in the patients exhibiting typical eclampsism, but also where it had been present prior to gestation, as in the chronically hypertensive patients in whom pregnancy provoked proteinuria. Although, in the latter instances, the sequence and nature of the clinical

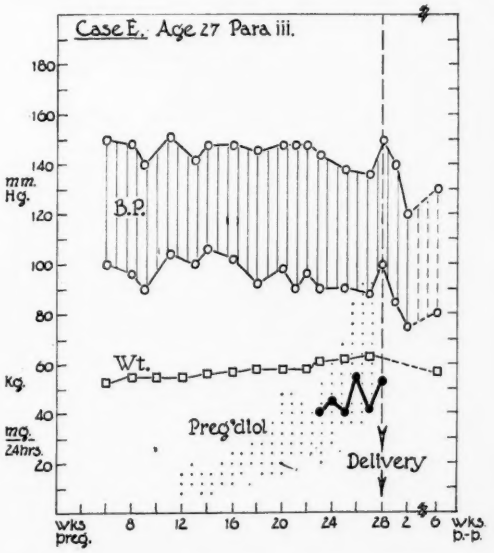
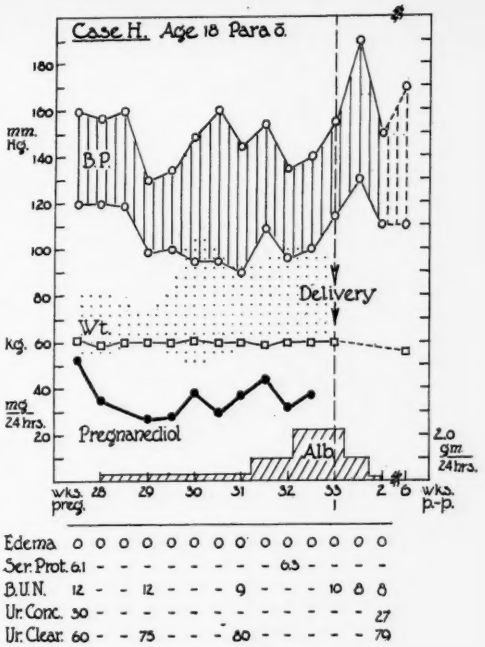


Fig. 3. PREGNANDIOL EXCRETION IN MULTIGRAVIDA EXHIBITING MILD CHRONIC HYPERTENSIVE DISEASE. (For explanation of symbols, see figure 2.) Note that excretion of pregnandiol is normal in a patient such as this one, wherein the moderate pre-pregnancy hypertension has not been aggravated by gestation, nor complicated by the development of edema or albuminuria.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Ur. Clear. 60 - - 75 - - - 80 - - - - - 70

Fig. 4. PREGNANDIOL EXCRETION IN PRIMIGRAVIDA EXHIBITING MODERATELY ADVANCED CHRONIC HYPERTENSIVE DISEASE. (For explanation of symbols, see figure 2.) Note fall in pregnandiol excretion coinciding with onset of albuminuria, although gestation failed to provoke edema or to aggravate pre-pregnancy arterial hypertension.

phenomena were never those of typical eclampsism, the abnormally low excretions of pregnandiol glucuronidate might indicate that such proteinurias were merely special forms of the latter disorder. We believe, however, that these proteinurias are essentially acute manifestations of the underlying chronic hypertensive disease, and that their precise relationship to eclampsism cannot yet be defined.

The association of diminished pregnandiol glucuronidate excretion and proteinuria in our patients was invariable; one was not encountered without the other. Moreover, when it was possible to detect the first appearance of both in the same patient, they were encountered simultaneously (fig. 2, 4). That the diminished amounts of pregnandiol glucuronidate found in the urine under these circumstances were not to be accounted for by technical failure to recover the compound completely in the presence of contaminating protein, was shown by our control experiments.

The depression of pregnandiol glucuronidate output in these disorders is probably due to faulty synthesis or conjugation of pregnandiol to form the glucuronidate, rather than to defective renal excretion. This is suggested by the fact that the similarly

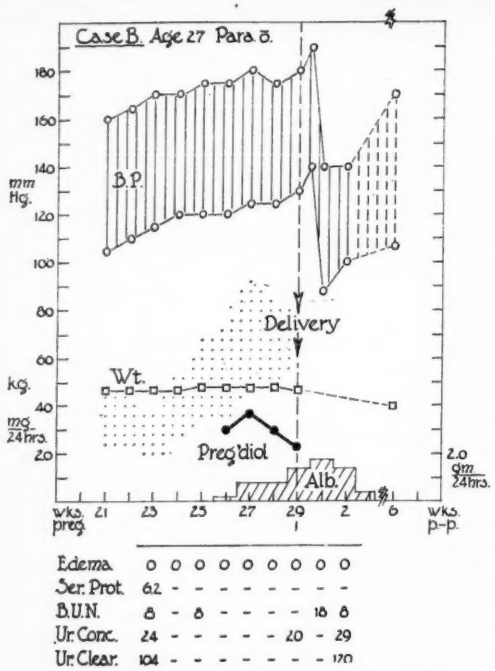

Fig. 5. PREGNANDIOL EXCRETION IN PRIMIGRAVIDA EXHIBITNG ADVANCED CHRONIC HYPERTENSIVE DISEASE. (For explanation of symbols, see figure 2.) Note low pregnandiol excretion during albuminuric period. Gradual aggravation of the arterial hypertension, temporary depression of renal concentrating function with slight elevation of blood urea nitrogen at the 29th week and persistence of albuminuria post-partum indicate a more severe grade of acute renal involvement resulting from gestation in this patient than in those illustrated in figures 3 and 4.

low concentrations of urine estrogen, found by several workers in patients suffering from eclampsism, is known to be associated with diminished blood estrogen levels (13, 14). The probability is therefore great that there is a diminished internal secretion of estrogen in this disorder, and a similar assumption seems valid for pregnandiol.

Caution must be observed in ascribing to pregnandiol glucuronidate or its precursors any determining role in the pathologic physiology of gestational hypertensions, for there is as yet no evidence that they play such a role. Abnormality of its excretion can, for the present at least, be regarded only as an associated phenomenon of such disorders.

SUMMARY

The urinary excretion of pregnandiol glucuronidate has been investigated in 10 parturient women exhibiting one or another of the following hypertensive disorders: pre-eclampsia; mild, uncomplicated chronic hypertensive disease; and severe chronic hypertensive disease complicated during gestation by the development of proteinuria.

The excretion of this compound is reduced below normal in the patients belonging to the first and last of these groups, but is unaffected in those with uncomplicated chronic hypertension. The abnormal depression of excretion in these patients first occurs at the onset of proteinuria, and is continuously associated with the latter phenomenon during the remainder of gestation.

The bearing of these observations upon the etiology of eclampsism, and upon the relation of this disorder to chronic hypertensive disease, is discussed.

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ENDOCRINE THERAPY OF FUNCTIONAL MENOMETRORRHAGIA AND OVARIAN STERILITY

I. THE CYCLIC ADMINISTRATION BY INJECTION OF ESTROGENS AND PROGESTERONE[1]

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THE MARITAL PLANS and maternal aspirations of younger women require the employment of all the conservative therapeutic approaches of a rational therapy when one desires to circumvent the ovarian failure responsible for irregularities of flowing and lowered fertility. The control of uterine hemorrhage by various empiric methods of hemostasis, however, may constitute at times expediential and quite appropriate therapy.

As commonly used by most clinicians, the various endocrine agents usually fall far short of effecting complete physiologic salvage in these conditions. This is true in particular of therapy which employs chorionic gonadotropins, estrogens, progesterone, androgens, stilbestrol or equine gonadotropins. This series of articles will deal with critical analyses of results obtained with various therapeutic schedules employed in the treatment of ovarian failure of women during the reproductive epoch.

One of us (E.C.H., 1) reported in 1936 that, whereas injections of estrogens given to patients bleeding from estrogenic endometria produced prompt hemostasis, injections of progesterone to similar patients were followed by an increased severity of flowing. Progestational alterations occurred in these circumstances only when both estrogens and progesterone had been given. These observations led to the formulation of a system of cyclic sterol therapy. Various reports from our clinic (2) have indicated that this form of therapy permitted the maintenance of cyclic bleeding in patients with functional menometrorrhagia. This report summarizes and evaluates our 4-year experience with this form of therapy.

Rationale of Sterol Therapy

The theoretical assumptions and the factual data, which support the use of sterols in ovarian failure, are summarized here.

I. With regard to the regulation of flowing.

(*a*) Estrogens check estrogenic bleeding and prevent its onset.

(*b*) Estrogens produce active endometrial proliferation which is necessary for the progestational responses to intrinsic progestin or injected progesterone. If inadequate estrogenic 'priming' of the endometrium is a factor in ovarian failure, adequate estrogenic therapy would remedy this.

(*c*) Estrogens, when given concurrently with progesterone, enhance the metabolism and endometriotropic activity of the latter sterol.

(*d*) Progesterone alters the metabolism of estrogens by facilitating the breakdown of estradiol into estrone and estriol and, thereby, increases the urinary excretion of estrogens (3). Disturbances in estrogenic metabolism doubtlessly characterize diverse grades of ovarian failure.

(*e*) The cyclic administration of adequate amounts of estrogens and progesterone permits initiation or

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reinstitution of normal endometrial cycles, which involve resumption of orderly responses of the vascular bed of the endometrium as well as of the peripheral vascular system disrupted by ovarian failure (4) and of characteristic epithelial phenomena of circulatory necrosis, desquamation and regeneration. This facilitates recovery of ovarian function by restoring normal conditions in the receptor organ (i.e., endometrium).

II. With regard to the reinitiation of cyclic ovario-pituitary reciprocities.

(*a*) If an endometriopathic disturbance in sterol metabolism is the primary cause of ovarian failure (such a cause probably would be mediated by way of the pituitary), cyclic therapy with estrogens and progesterone by its endometrial action (vascular and epithelial) may correct this.

(*b*) When the failure is intrinsic to the ovary (refractivity due to immaturity, incomplete puerperal recovery, senility or infection) sterol therapy is substitutional and only complements the deficit. By maintaining normal endometrial cycles, however, in some instances spontaneous recovery of ovarian function may be facilitated.

(*c*) When ovarian failure is due to endometriopathic factors or intrinsic ovarian inadequacy, secondary alterations of quantitative and qualitative nature doubtless arise in the pituitary. The cyclic administration of sterols 'conditions' the pituitary and maintains its coordination with ovarian and endometrial cycles; this effect further facilitates recovery of normal reciprocities.

(*d*) When ovarian failure is due to hypogonadotropic functions of the pituitary, cyclic sterol therapy while not capable of fulfilling complete salvage, may permit cyclic bleeding with normal endometrial responses during intervals between series of cyclic gonadotropic therapy.

(*e*) If significant pituitary failure exists, substitution at the ovarian level with cyclic sterols, is more practical and effective than substitution at the pituitary level with cyclic gonadotropins. In these instances, cyclic gonadotropins may be reserved for attempts at conception.

(*f*) When disturbed thyroid function is the primary cause of ovarian failure, the employment of cyclic sterols may permit adequate substitution for ovarian function until such time that thyroid function may be brought to normal: this use of sterol therapy may allow satisfactory handling of functional menometrorrhagia due to hypothyroidism without recourse to curettage.

Therapeutic Regime

Various combinations of sterols in diverse dosages were employed in order to evaluate pharmacologic effectiveness of the different schedules. In general, due to the observations of Smith and Smith (3) on estrogenic metabolism, we used estradiol or estradiol benzoate or dipropionate during the first half of the cycle and estrone or estriol glucuronide together with progesterone during the latter half of the cycle. The following schedules were employed:

(*a*) *Estrogens followed by progesterone* (*e*→*p*).[3] Immediately following the cessation of flowing, or on the 7th day of flowing if it still continued, injections of estrogens[4] were started. Estrogens, as a rule, in daily amounts of 2,000 R.U. of estradiol benzoate or dipropionate (or 10,000 I.U. of estrone) were given for 10 to 14 days. This was followed immediately by daily injections of 5 to 10 mg. of progesterone for 7 to 10 days. Injections of progesterone were discontinued if bleeding intervened, lest excessive flowing be produced.

(*b*) *Estrone or estradiol benzoate and progesterone administered concomitantly* (*e*+*p*).[3] Estrone commonly or estradiol benzoate or dipropionate was the estrogen of choice. Injections were started on the 14th day of the cycle. Estrone 10,000 I.U. (or estradiol benzoate or dipropionate 2,000 R.U.) and progesterone 5 to 10 mg. were given daily for 10 to 14 days. treatment was discontinued if bleeding intervened.

(*c*) *Estrogens followed by estrogens and progesterone administered concomitantly* (*e*→*e*+*p*).[3] This schedule is a combination of (*a*) and (*b*) substituting the concomitant administration of estrogens and progesterone for that of progesterone alone.

(*d*) *Progesterone* (*p*). Injections were begun on the 14th day of the cycle as in (*b*) and progesterone in daily doses of 5 to 10 mg. was given for 10 to 14 days.

(*e*) *Estriol glucuronide and progesterone administered concomitantly* (*es*+*p*).[3] This schedule is essentially the same as (*b*) except that estriol glucuronide given orally was the estrogen employed. The usual daily dosage of estriol glucuronide was 1,440 day O.U.

(*f*) *Estradiol benzoate or dipropionate followed by estriol glucuronide and progesterone administered concomitantly* (*e*→*es*+*p*).[3] This schedule is essentially a combination of (*a*) and (*e*) with the substitution of the concomitant administration of estriol glucuronide and progesterone for that of progesterone alone.

The general procedure of therapy in all these schedules has been the same. Patients, who were experiencing prolonged or excessive episodes of bleeding when first seen, secured remissions from bleeding either by curettage or by large doses of estrogens

[3] These abbreviations will be employed in the presentation of clinical data to designate these various therapeutic schedules.

[4] Estradiol usually was employed as the estrogen of choice, chiefly as the benzoate. In some instances the dipropionate was used. A number of cycles of therapy, however, was carried out using estrone.

(2,000 to 6,000 R.U. of estradiol benzoate or dipropionate or 10,000 to 30,000 I.U. of estrone daily).

When bleeding began before a scheduled cycle of therapy had been completed, all therapy was discontinued for 7 days; at the end of this time, therapy was resumed if indicated. If bleeding continued at the end of the 7 days, estrogens were given to check it. If no bleeding followed a series of therapy, another series of treatments was started at the end of the 7 days of rest.

The number of cycles of therapy given a patient was not a fixed one. In general, therapy was given until cyclicity was reestablished and, in many instances, until progestational alterations were induced in the endometria.

METHODS OF STUDY

Pretreatment levels of ovarian function were estimated from studies of endometrial biopsies secured within the first 12 to 18 hours after the onset of episodes of bleeding. When patients had required curettage or estrogens for temporary hemostasis, treatment was postponed until ovarian levels were determined by biopsies taken at subsequent spontaneous flowings. In some instances, urinary titers of sodium pregnandiol glucuronide (estimated by Venning's method, 5) and of 17-ketosteroids (estimated colorimetrically by Oesting's method, 6, after preliminary extraction by the method of Cuyler and Baptist, 7) were determined during pretreatment and treatment cycles. All patients chosen for these studies bled prior to therapy from estrogenic endometria.

Endometrial responses during therapy were studied from biopsies taken at the onsets of bleeding in the majority of instances.

Evaluation of the immediate effects of therapy was based upon: regulatory effects on the cyclicity and the amount of bleeding; specific alterations induced in the endometrial responses; and changes induced in the urinary excretion of the pregnandiol-complex and the 17-ketosteroids. These observations were made during actual course of therapy.

Evaluation of the ultimate effects of therapy was based upon: the character and cyclicity of bleeding following discontinuation of therapy; the endometrial responses which characterized no treatment cycles which followed discontinuation of therapy (the finding of progestational responses at this time, when patients had bled from estrogenic endometria prior to therapy, was interpreted to represent a therapeutic restoration of normal ovario-endometrial reciprocities); and the occurrence of pregnancies following discontinuation of therapy.

CLINICAL DATA

A total of 51 patients, whose average age was 22.7 years, was treated by this form of therapy. None of these patients exhibited any symptoms or signs of endocrine disease except irregular flowing and ovarian sterility. Forty-six of these patients bled from estrogenic endometria. All of these patients were chosen for conservative therapy because of their marital status or maternal aspirations. The bulk of the patients experienced menometrorrhagia, although some of those whose primary complaint was sterility described infrequent episodes of bleeding. A composite summary of the clinical data of these 51 women is presented in table 1.

Preliminary hemostasis. Twenty of the 51 patients required curettage, while the remainder either did not need immediate hemostasis or secured it from estrogenic therapy.

Number and distribution of cycles of therapy. A total of 217 cycles of therapy was given. The largest number of cycles given a patient was 10 (in 3 instances); the smallest number was 1 (in 8 instances).

The distribution of therapeutic schedules according to kind and frequency of employment was as follows.

Treatment formula	Total No. of cycles	Total No. of cycles in which endometrial responses were studied
e→p	62	56
e+p	50	39
e→e+p	46	37
p	46	33
es+p	5	4
e→es+p	8	4

Dosage of progesterone. Cyclic dosages of progesterone varied from 5 to 260 mg. Cyclic dosage, ranging from 25 to 50 mg. was given in 171 instances or during 78.8% of the cycles. The total amount of progesterone used was 8,965 mg; the average cyclic dosage was 41.3 mg. The average dosage of progesterone given during cycles of therapy in which endometrial responses were evaluated was 40.4 mg.

Cyclicity and duration of flowing during therapy. Data upon the regulatory effects upon bleeding are presented in figure 1.

The average length of the cycle during therapy was 27.5 days and the average duration of flowing was 5.8 days.

Endometrial responses prior to therapy. Forty-six of the 51 patients permitted evaluation of endometrial responses to therapy, since they bled from estrogenic endometria prior to the initiation of therapy. The distribution of the endometrial findings of these 46 patients, according to kind and frequency of occurrence was as follows.

Hypoestrogenic	3 patients	6.5%
Persistent estrogenic	30 patients	65.2%
Hyperestrogenic	13 patients	28.3%

TABLE 1. COMPOSITE CLINICAL DATA OF THE 51 PATIENTS TREATED BY CYCLIC STEROLS GIVEN BY INJECTIONS

Case No.	Age	Menstrual history	Endometrium at bleeding before treatment	Nature of treatment and endometrial responses associated with bleeding during therapy	Endometrium at bleeding after treatment	Follow-up data
I	30	Ol	E	E35(e→p) E35(e→p) E−35(e→p) E−50(p)	E−	OR 32 mo.
II	25	Ol	E	E−35(e→p) M35(e→p) O35(p) M25(e→p) E10(e→p) E50(e→e+p) E50(e→e+p) E45(e→e+p) E50(e+p) E35(e+p)	O	OR 19 mo.
IV	23	Ol	E	E35(e→p) E+35(e→p) E35(e→p) E40(p) E50(p) E50(p)	O	OR 21 mo.
V	19	Mm	E+ ↓	E35(e→e+p)	O	OR 24 mo.
VII	20	Mm	E ↓	O15(e→p) E10(e→p) E5(e→p) E10(e→p) E20(p) E10(p) E25(p) E30(p) M15(p)	O	OR 22 mo.
IX	16	Mm	E+ ↓	E35(e→p) E35(e→p) E35(e→p) M40(e→p) E40(p) E35(e→p) E50(p) M25(e→p) O50(e+p) M40(e+p)	M	→OS
X	31	Mm	E ↓	O40(p) E35(e→p)	O	OR 25 mo.
XI	26	Mm	E ↓	E35(e→p) E35(e→p) E35(e→p) E35(e→p) E35(p) E50(e+p) M50(e+p) E40(e+p) O35(e+p)	E+	→OS
XII	16	Mm	E	E+35(e→e+p) O35(p) E30(p) M50(p) E35(e→e+p) E45(e→p) E50(e→e+p) M50(e+p) M50(e+p) M30(e+p)	PP	Pregnancy
XIII	12	Mm	E+	M35(p) M35(p) E35(p) M35(p) E50(p) M50(p) O50(p) M50(e+p) M50(e+p)	E	OR 18 mo.
XIV	20	Mm	E	O10(e→p) E15(e→p)	O	OR 23 mo.
XV	23	Mm	E+ ↓	E35(p) E30(e→p) O20(e→p) M35(e→p) O35(e→e+p) E30(e→e+p) O35(e→e+p)	E	→OS
XVI	16	Mm	E+ ↓	M35(p) E45(p) E45(p) O45(p) E30(p) O50(p)	E	OR 19 mo.
XVII	28	Ol	E	E+30(p) E+35(e→e+p) O35(p) E25(e→e+p) E45(e+p) E50(e+p) E50(e+p) E50(e+p) M40(e+p)	M	→OS
XVIII	23	Ol	E	E35(e→e+p) E35(e→e+p) E35(e→e+p)	O	OR 19 mo.
XX	20	Mm	E	M50(e→p) E35(e→p) O25(e+p) M35(e+p) O35(e+p)	O	OR 17 mo.
XXI	18	Mm	E+	O30(e→p) M25(e→p) M40(e→e+p) E30(e→p) E50(e+p) E50(e+p) O50(e+p) M50(e+p)	PP	Pregnancy
XXII	31	CyS	E	O15(p) O15(p) E60(p) O40(p) M40(p)	PP	Pregnancy
XXIII	17	Mm.	E ↓	E10(e→p) E20(e→p) M20(e→p) M40(e→p)	M	→OS
A2	18	Mm	E	M40(e→e+p)	M	OR 14 mo.
A3	21	Mm	E+ ↓	M50(e+p) E35(e+p)	O	OR 15 mo.
A4	38	Mm	E+ ↓	M20(e→e+p) O50(e+p) E40(e+p) E50(e+p)	E	→OS
A5	16	Mm	E+ ↓	O25(e+p) M25(e+p) O25(e+p)	O	OR 14 mo
A7	19	Mm	E ↓	M50(e+p) E50(e+p) M50(e+p) P50(e+p)	M	OR 15 mo.
B4	30	Ol	E−	E−35(e→p) E−30(e→p) E−35(e→p) E−25(e→p)	E−	OR 22 mo.
B5	18	Ol	E−	O15(e→e+p) E45(e→e+p) E35(e→e+p) E15(e→e+p)	E−	→CyG
B6	19	Mm	E+	E25(e+p) E−10(e+p) E50(e+p) E15(e→es+p)	E	→OS
B7	28	Mm	E	M10(e→p)	O	→OS
B8	20	Mm	E ↓	O40(e→es+p) *35(e→es+p) E20(es+p) M26c(es+p) E90(es+p)	E	→CyG.
B9	30	Ol	E−	E−120(e→p)	E+	→CyG
B10	29	Mm	E+	P50(e→e+p) O30(e+p) O20(p) E15(e+p) O160(e→es+p) O220(p) O90(p)	M	→OS
B11	21	Mm	E ↓	E40(e→p)	E	OR 5 mo.
B12	14	Mm	E+	O30(e→e+p) E+10(e→e+p) E25(e+p) E70(e→p) E80(es+p)	O	OR 10 mo.
B13	16	Ol	E	E55(e→e+p) O75(e+p)	O	→CyG
B14	15	Mm	E+ ↓	E+30(e→p) E110(e→p) E90(e→p)	O	→CyG
B15	19	Mm	E	E40(e(+es)→e+p) E35(e+p)	O	OR 11 mo.
B17	28	Ol	E	E70(e→e+p) E60(e→e+p)	O	→CGP
B18	30	Ol	E	M45(e→e+p) M70(e→e+p) O50(e→e+p)	O	OR 2 mo.
B19	26	Mm	E ↓	E70(e→e+p)	O	→OS
B20	29	Mm	E	M50(e→e+p)	O	OR 3 mo.
B21	19	Mm	E	O60(es+p) E50(e+p)	O	→CGP
B22	32	Mm	E	M10(e→e+p) O50(e→e+p) M70(e+p)	O	OR 1 mo
B23	15	Mm	E	E50(e→e+p) E30(e→p)	O	→OS
B24	13	Mm	E	E40(e→e+p) E70(e→p)	O	OR 7 mo.
B25	24	Mm	E ↓	*70(e→e+p)	O	→OS
B16	28	CyS	E	M55(e→es+p) O35(e→es+p) M50(e→es+p) E50(e→p)	P	→CyG
III	22	Mm	M	E10(e→p) E10(e→p) E5(e→p) O5(e→p) M45(p) E25(p) E25(p) O40(e→e+p)	E	OR 27 mo.
VI	17	Mm	M ↓	E40(p) E35(e→e+p) E−35(e→p) E35(e→e+p) O35(e→e+p) E35(e→p) E35(e→p)	E	OR 27 mo.
VIII	37	CyS	M ↓	O35(e→p) E35(e→e+p)	O	→CyG
XIX	26	Mm	M	M65(e+p) E45(e→e+p) P40(e+p)	O	OR 14 mo.
B1	30	CyS	M	E35(e→e+p) M50(e→e+p) M45(e→e+p) O70(e+p)	O	→CyG

Menstrual history: Ol, oligomenorrhea; Mm, menometrorrhagia; CyS, cyclic bleeding sterility. Endometrium at bleeding before, during and after treatment: ↓ curettage prior to therapy; E−, hypoestrogenic endometrium; E, persistent estrogenic endometrium; E+, hyperestrogenic endometrium; M, mixed progestational endometrium; P, normal progestational endometrium; PP, progestational endometrium, presumed due to the occurrence of pregnancy; *biopsy, insufficient tissue obtained; O, no biopsy. Nature of treatment and associated endometrial responses: Numerals following endometrial responses indicate total cyclic dosage of progesterone in mg.; the treatment formulae given in parentheses for each cycle have been explained under *Therapeutic regime*. Follow-up data: OR, followed by number of months indicates that no further treatment has been given during the specified intervals of months; →OS indicates that the patient was transferred to cyclic sterol therapy orally administered; →CyG indicates that the patient was transferred to cyclic gonadotropic therapy; →CGP indicates that the patient was transferred to cyclic therapy with chorionic gonadotropins and progesterone.

Endometrial responses during therapy. The composite data assembled in table 1 give the individual responses of each patient. Figure 2 presents the incidence of the various endometrial patterns prior to, during and after the discontinuation of therapy.

The distribution of the endometrial findings of the 46 patients during 154 sampled cycles of 193 cycles of therapy was as follows.

Hypoestrogenic	9 occurrences	5.9% incidence
Persistent estrogenic	94 occurrences	61.0% incidence
Hyperestrogenic	6 occurrences	3.9% incidence
Mixed progestational	43 occurrences	29.2% incidence
Normal progestational	2 occurrences	

The 45 progestational responses observed during therapy followed doses of progesterone which ranged from 10 to 260 mg. Thirty-six or 80% of these responses followed dosages which ranged from 25 to 50 mg. As a rule, large doses of progesterone were relatively ineffective: no progestational responses were induced by 80 mg. (1 cycle), 90 mg. (2 cycles), 110 mg. (1 cycle) and 120 mg. (1 cycle). The average dosage of progesterone associated with progestational responses was 45.1 mg.; this corresponded well with the average dosage of 40.3 mg., given during the cycles of therapy in which endometrial responses were sampled.

The correlation of the character of the therapeutic schedule with the occurrence of progestational responses was as follows.

Treatment formula	No. of cycles given in which endometrial responses were studied	Occurrences of progestational responses	% yield of progestational responses
e→p	50	10	20.0
e+p	37	16	43.2
e→e+p	31	8	25.8
p	28	8	28.5
es+p	4	1	25.0
e→es+p	4	2	50.0

Effects of therapy upon urinary excretion of 17-ketosteroids and pregnandiol complex. The urinary excretion of 17-ketosteroids was investigated prior to therapy during 7 cycles of 7 patients. The average daily values for different patients ranged from 24 to 93 I.U. The average daily value for the group was 53 I.U. Similar determinations were done during 5 cycles of 4 patients under therapy. The average daily values for different ones of these patients ranged from 11 to 46 I.U. The average daily value for the group was 25 I.U.

The urinary excretion of sodium pregnandiol glucuronide was investigated during 13 cycles of 12 patients, prior to therapy. The total cyclic excretion ranged from 0 to 136 mg. for individual patients. The average cyclic excretion for the group was 28 mg. Similar determinations were done during 26 cycles of 9 patients under therapy. The total cyclic excretion per patient ranged from 0 to 51 mg. The average cyclic excretion for the group was 22 mg.

Endometrial responses following discontinuation of therapy. Biopsies were made on 22 patients at the onsets of episodes of bleeding which followed cycles of no therapy. The endometria of 16 of these patients had shown progestational responses during therapy, while those of the other 6 had failed to do so.

The distribution of the endometrial responses of these 22 patients according to kind and frequency of occurrence was as follows.

	Patients
Hypoestrogenic	3
Persistent estrogenic	7
Hyperestrogenic	2
Mixed progestational	6
Normal progestational	1
Normal progestational (presumed due to pregnancy)	3

These data indicate an incidence of 45.5% progestational endometria after discontinuation of therapy. All of these 10 progestational responses occurred in the group of 16 patients whose endometria gave progestational responses during therapy, an incidence of 62.6% progestational response after therapy in this group.

The possible incidence of progestational responses after discontinuation of therapy may be estimated for the entire group of 46 patients as follows: assuming that none of the 21 patients who failed to show progestational responses during therapy would have shown progestational responses after the discontinuation of therapy and likewise assuming that the 25 patients whose endometria showed progestational responses during therapy would have yielded the same percentage incidence of progestational responses after therapy as the 16 investigated (i.e., 62.6%), the number of progestational responses obtained would have been nearly 16; the occurrence of progestational endometria in approximately 16 of the 46 patients would equal an approximate 35% incidence.

Clinical course of patients after discontinuation of therapy. The clinical course of patients after discontinuation of therapy has been rendered difficult of evaluation in certain instances due to a deliberate transfer of patients to other therapeutic schedules. Such a transfer aimed at possible segregation of groups of 'reacters' to different therapeutic measures. The data secured in this manner will be analyzed in subsequent papers of this series. Strictly clinical considerations prompted us to give additional therapy at times when our scientific interests would have justified critical evaluation of treatment previously given before proceeding further with new therapy.

The follow-up data on the 21 patients whose endometria showed no progestational responses during

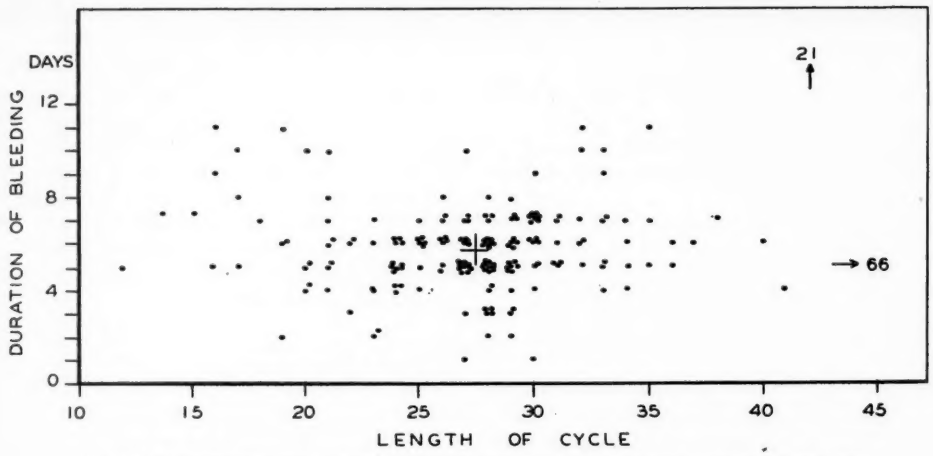

Fig. 1. The lengths of cycles and the durations of bleeding during injected cyclic sterol therapy.

therapy or after its discontinuation are summarized here.

Ten received additional therapy and continued to bleed cyclicly (4 cyclic sterols orally, 2 cyclic chorionic gonadotropins and progesterone, 4 cyclic gonadotropins).

One has not reported since discontinuation of therapy 32 months previously; the endometrium of this patient after the end of treatment was of persistent estrogenic nature.

Three have reported cyclic bleeding of normal amounts for 12, 12 and 19 months respectively.

Six have reported return of oligomenorrhea which characterized their menstrual histories prior to therapy. Treatments had been discontinued 23, 22, 21, 19, 18 and 14 months previously.

One required additional sterol therapy for menometrorrhagia 7 months after cessation of first series of treatment. The subsequent response was satisfactory.

The follow-up data of the 25 patients whose endometria showed progestational responses during therapy and who yielded the 10 patients with progestational responses after discontinuation of therapy is summarized here.

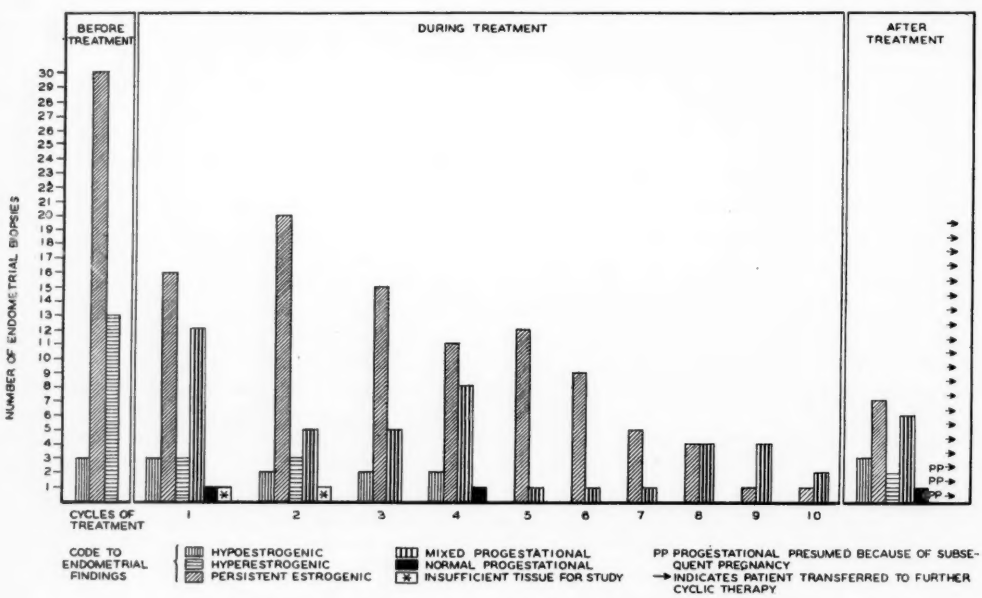

Fig. 2. Endometrial responses before, during and after injected sterol therapy.

Three became pregnant. One is approximately 2 months' pregnant. Another is approximately 4 months' pregnant. The third delivered a healthy child 10 months previously.

Ten received additional therapy and continued to bleed cyclicly (8 cyclic sterols orally; 2 cyclic gonadotropins).

Two have completed treatments too recently to warrant follow-up evaluation.

Three have not reported since discontinuation of therapy 3, 5 and 14 months previously; one of these patients had a persistent estrogenic endometrium on follow-up biopsy.

Three have had cyclic bleeding in normal amounts for intervals varying from 14 to 17 months since discontinuation of therapy.

Three have had return of oligomenorrhea which characterized their menstrual histories prior to therapy. Treatment had been discontinued 3, 14 and 19 months previously.

One required further therapy for menometrorrhagia, 13 months after cessation of first series of treatment.

From this latter group of 25 patients, the follow-up data upon the 10 patients, who showed progestational responses after the discontinuation of therapy, are segregated and reported as a single group.

Three became pregnant.

Four were transferred to oral cyclic therapy. In one instance no interval elapsed between discontinuation of injected cyclic sterol and initiation of oral cyclic sterols (i.e., the patient began the latter form of therapy with a mixed progestational endometrium). In instances of the other 3 the progestational responses had reverted to estrogenic ones prior to the initiation of therapy. The elapsed interval between the two therapies was 5 months in one instance; during this time 3 mixed progestational responses were secured and were followed by an estrogenic endometrium just prior to the initiation of oral sterol therapy. In the instances of the other 2 patients, only 2 cycles intervened before oral sterol therapy was started.

One patient stopped sterol therapy 8 months ago and was transferred to cyclic gonadotropic therapy.

Two patients stopped therapy 14 and 15 months ago. One had cyclic bleeding for 5 months but has not reported recently. The other patient has not reported since treatment stopped.

The follow-up data of the 5 patients who began sterol therapy with mixed progestational endometria are summarized for sake of completeness and for comparison with the previous group.

The progestational endometria of 2 of these patients reverted to estrogenic ones after cessation of therapy, 21 and 27 months previously. A follow-up endometrial study of 1 patient showed continued progestational responses; the patient was treated subsequently with cyclic gonadotropins. The other 2 patients did not report for follow-up biopsies; one was transferred subsequently to cyclic gonadotropic therapy without a pretreatment endometrial study; the other patient has not reported any data since cessation of therapy 14 months previously.

None of the 51 patients treated by this form of therapy subsequently has required surgical or roentgenologic measures to control their irregularities of bleeding.

DISCUSSION

This method of therapy permits an uniformly successful means of regulating bleeding in menometrorrhagia and oligomenorrhea. This effect is independent of the induction of progestational responses in the endometria. It is due doubtlessly to direct vascular effects, principally upon the spiral arterioles. When menometrorrhagia existed prior to therapy, this regulatory effect commonly continued after discontinuation of treatment and despite the occurrence or non-occurrence of progestational alterations. When oligomenorrhea existed prior to therapy, there was observed almost uniformly a prompt return of this irregularity when treatment was stopped. This observation suggests the likelihood that there is a significant difference in the vascular pathology of these two types of irregularities.

The symptomatic control of functional menometrorrhagia is a necessary part of any therapy. Usually it is secured by curettage or uterine packing. The regulation of bleeding permitted by this therapy is conditioned only by the duration of treatment. While a firm control of bleeding is maintained, diagnostic procedures may be carried out at leisure, effects of hemorrhage may be repaired and various therapeutic measures aimed at more permanent results may be instituted. By this method, curettages of adolescent patients may be avoided and the patient permitted to carry on her daily duties without a condition of semi-invalidism intervening.

A characteristic variability in the frequency of occurrence of progestational responses has been observed throughout our experience with this form of therapy. In previous reports by some of us (8) this inconstant response was related to inadequate metabolism and utilization of progesterone and to endometriopathies which interfered with the normal endometriotropic activities of these sterols. Most of the reports of the pharmacologic effects of estrogens and progesterone upon the endometria of castrates, except those of Elden (9), lead to the expectation of constant progestational responses in patients of the type treated. Sufficient data are available upon diverse therapeutic schedules and varying doses of progesterone to discount inadequate therapy as a factor in these failures of response. While the employment of estrogens and progesterone concurrently has increased the frequency of progestational responses, their incidence of occurrence has not approached 100%. We believe this peculiar alteration in sensitivity of the endometria is an expression of an endome-

triopathy, which is an integral part of the functional pathology of the ovario-endometrial failure. Such an endometriopathy would render hazardous at times the use of the endometrium as a mirror of ovarian function (10). The failure of 21 of the 46 patients to experience any progestational responses during therapy seems most likely related to inadequate treatment. It seems difficult to envision an absolute endometrial refractivity except when traumatism and destruction by chemicals and roentgen therapy are factors of genesis.

Proof has been submitted that at least 10 of the 46 patients treated experienced a return of fairly complete ovarian function as a result of therapy. Past experience with this group of patients and many other similar ones convinces us that these responses were not due to chance or spontaneous recovery of function. Explanation of this therapeutic salvage requires the assumption that this form of therapy in some manner overcame the cause or causes responsible for ovarian failure in this particular group of patients. Correlational studies made by some of us in the past (11) warrant the belief that endometrial failure exists very infrequently without concomitant alterations in ovarian and pituitary functions. When marked ovarian failure exists, as during the climacteric, compensatory hypergonadotropic activity of the pituitary occurs. When an endometriopathic failure of proper metabolism, utilization and excretion of estrogens precipitates ovarian failure, gonadotropic activity of the pituitary may be lowered due to these disturbances in sterol metabolism. In this latter condition cyclic sterol therapy may be capable of effecting a return of normal function by (*a*) overcoming the endometriopathy, as judged by the occurrence of progestational responses during therapy and (*b*) by conditioning gonadotropic functions of the pituitary through facilitating estrogenic metabolism and excretion and by the direct biphasic effects of the cyclic sterols administered on the pituitary. Data to be presented in a later paper of this series tend to substantiate the specificity of salvages obtained from sterol therapy: certain patients are salvaged by sterol therapy who failed to respond to cyclic gonadotropic therapy and vice versa.

To what extent these salvaging effects are due to estrogens alone and to what extent they are due to progesterone is difficult to decide. We believe that both sterols play a role in this process. We have encountered evidence, however, that under certain conditions progestational responses have followed the use of estrogens alone. (Some of these data will be presented in a later paper of this series.) We have reported recently (12) data to support the view that moderate doses of estrogens given intermenstrually not only fail to depress the corpus luteum function of healthy women, but even tend to amplify this function. Clauberg (13) and Westman (14) have observed that estrogens given midmenstrually may increase corpus luteum function or even induce ovulation (Clauberg). Allen and Heckel (15) have made similar observations regarding prolongation of corpus luteum function in the rabbit.

The data presented indicate that salvage obtained by this therapy is not necessarily permanent; i.e., the ovarian failure may recur. The same fact is true doubtlessly of that secured by cyclic gonadotropins. (Reported in subsequent paper of this series.) There is no ground for expecting unsatisfactory results from additional therapy in these instances.

These observations apparently permit a definite negative answer to those workers who fear possible depressing effects on ovarian function from this form of therapy. No untoward, constitutional or local responses have occurred in any of the patients treated, despite the fact that, in all, as much as 35 to 50 cc. of vegetable oils (solvents for sterols) have been injected intramuscularly each month for as long as 6 months. No evidence of any liver or renal damage from these sterols was encountered.

The depression of the urinary values for 17-ketosteroids which occurred during therapy is in line with observations previously reported by some of our group (16) that estrogens, given orally or parenterally, lower these titers. The minimal alterations which occurred in urinary titers of sodium pregnandiol glucuronide during therapy coincide with previously reported experiences of members of our group (17). These experiences have led us to regard the method of Venning as being of value only when the metabolism of intrinsic progestin is being studied; it is of doubtful value in the study of the metabolism of extrinsic progesterone.

These data have indicated that the doses of progesterone employed have been adequate. Poor and infrequent progestational responses during therapy led us at an early stage of these studies to question the sufficiency of our dosage. It is significant, we believe, that no toxic effects were observed from monthly doses of progesterone as large as 260 mg. Patients who received these larger doses showed more disturbance in water balance prior to bleeding than those receiving smaller amounts, i.e., a gain of 3 to 5 pounds due to menstrual edema was not uncommon. As a rule, these patients reported low-grade lower abdominal cramping during the entire time large doses of progesterone were administered. Although our data indicate that the most effective dosage range for progesterone was from 25 to 50 mg. per month, the assumption is not warranted that smaller amounts would not be equally effective, since relatively few small doses of progesterone were employed.

There is a clear-cut differential regarding the effectiveness of the various therapeutic schedules. The highest yield of progestational responses was given by the e+p formula, i.e., estrogens and progesterone given concurrently during the latter 10 to 14 days of the cycle.

While our primary purpose in arranging the various therapeutic schedules was to employ such doses which would prove adequately large to permit a thorough evaluation of this method of therapy, we have not been unmindful of its possible adoption as a method of practical therapeutics. The present cost of the sterols in the doses employed in most of the treatment schedules described renders the program too expensive for the average patient. The necessity for repeated injections at frequent intervals for some months puts a heavy burden upon the patient and physician. We feel fairly confident that decreases in dosages and simplification in regime can be made without any significant sacrifice of effectiveness. The following schedule is suggested as an example of such a modification.

Following hemostasis induced by estrogens, estradiol benzoate or dipropionate in 2,000 R.U. doses is given daily for 10 to 14 days; this is followed by progesterone and estradiol benzoate or dipropionate in doses of 5 mg. and 2,000 R.U. respectively given every other day for 10 to 14 days. Following bleeding, (which if it tends to be prolonged may be checked with estrogens) subsequent cycles of therapy may embrace only the latter part of the therapy given during the first cycle, i.e., estrogens and progesterone from the 14th to the 24th or 28th day of the cycle. At least 4 cycles of therapy should be given before rest and test of possible readjustment of ovario-endometrial responses are attempted. (If therapy follows curettage, all cycles of therapy may be given according to the latter ones.) Less rigid therapy may permit adequate handling of patient, but probably not without some irregularities intervening. The program described is not too expensive or too onerous for practical adoption.

As subsequent reports in this series of papers will indicate, occasions arise when the combined use of this therapy with thyroid substance or cyclic gonadotropins for their specific effects on oögenesis and ovulation is highly desirable. No method free from undesired sequelae permits such effective control of bleeding, as does the use of sterols. Proponents of androgenic therapy in functional bleeding have offered no proof of ultimate salvage from that form of therapy; its hemostatic effects seem established but also its 'ovarian negating' and virilizing ones.

We feel that the data submitted justify the following deductions. Cyclic sterol therapy is an effective method of regulating bleeding in functional menometrorrhagia. Full recovery of ovarian function may follow its use in a certain group of patients, whose ovarian failure is related to an endometriopathic disturbance in sterol metabolism. In other instances, in which the primary cause of ovarian failure is thyroid or pituitary deficiency, cyclic sterol therapy may prove a valuable adjunct to use of thyroid substance or gonadotropins. Conversely, this therapy has no depressing effects on ovarian function.

SUMMARY

A group of 51 young women, average age 22.7 years, with menometrorrhagia and ovarian sterility characterized by bleeding from estrogenic endometria was treated by the cyclic administration of estrogens and progesterone. A total of 217 cycles of therapy was given, an average of 4.2 cycles per patient. Immediate responses to therapy were judged by alterations in the duration and cyclicity of bleeding and by specific responses of the endometria, as evidenced by biopsies taken at the onset of episodes of bleeding. Ultimate therapeutic salvage was evaluated by the continuation of cyclic bleeding, by the spontaneous recurrence of normal ovario-endometrial cycles and by the occurrence of pregnancies after the discontinuation of therapy. Some patients fulfilled all these criteria for therapeutic salvage. 45.5% of the patients investigated by endometrial biopsies after the discontinuation of therapy showed spontaneous occurrences of progestational cycles. In this group there were three normal pregnancies. The modus operandi of this form of therapy is discussed. It is suggested that therapeutic salvage is due to a favorable influence of the sterols on some theoretical endometriopathic disturbance in sterol metabolism.

We are indebted to a number of commercial organizations for supplying the large quantities of sterols required for these studies.

The bulk of the progesterone used was supplied as proluton by Schering Corporation, Bloomfield, New Jersey. Liberal amounts of progesterone were supplied also by: Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey (lutocylin); Eli Lilly Company, Indianapolis, Indiana (progestin); Winthrop Chemical Company, Atlanta, Georgia office (C. L. P.).

Estradiol benzoate was supplied by Schering Corporation, Bloomfield, New Jersey (progynon-B) and by Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey (ben-ovocylin). Estradiol dipropionate (di-ovocylin) was supplied by Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey.

Estrone was supplied by Parke, Davis & Company, Detroit, Michigan (theelin) and by E. R. Squibb & Sons, New York City (amniotin).

Estriol glucuronide was supplied as powdered sodium estriol glucuronide and as emmenin by Ayerst, McKenna & Harrison, Montreal, Canada.

ADDENDUM

Patient XXIII who received her last therapy October, 1938, and who was counted as a therapeutic salvage, returned to the Obstetrical Clinic January 27, 1941, and was found upon examination to be 7 months' pregnant. This gives an incidence of 4 pregnancies among the 10 patients reported as salvaged by this form of therapy.

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ENDOCRINE THERAPY OF FUNCTIONAL MENOMETRORRHAGIA AND OVARIAN STERILITY

II. ORAL USE OF ANHYDRO-HYDROXY-PROGESTERONE AND ESTROGENS[1]

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INHOFFEN AND HOHLWEG (1) described in 1938 the preparation of pregnen-in-on-3-ol-17 (anhydro-hydroxy-progesterone; 17-ethinyl testosterone) rom estradiol. These workers reported that, when this compound was injected into immature mice, which had been treated previously with estrogens, it was approximately one-third as effective in producing progestational alterations as was synthetic progesterone, similarly administered. They observed, however, that when the sterol was given by mouth to similar animals, it was approximately 15 times as potent as progesterone given orally.

In May, 1939, one of us (E.C.H.) (2) reported that anhydro-hydroxy-progesterone (pregneninonol) had been employed orally in the treatment of menometrorrhagia with promising results and that, while fairly large doses had been employed, no evidences of any toxicity had been encountered. Evidence was submitted that this sterol was capable of causing progestational alterations in the endometria of women. Additional pharmacologic similarities of anhydro-hydroxy-progesterone were established by Salmon, Walter and Geist (3) and by Zondek and Rozin (4). The former group of workers showed that progestational differentiation of postmenopausal endometria could be produced by orally administered anhydro-hydroxy-progesterone. The latter workers reported that intermenstrual hemorrhages could be induced by similar therapy.

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[2] Ciba Fellow in Clinical Endocrinology.

A recent report by some members of our group (5) described the results of the cyclic administration of anhydro-hydroxy-progesterone or of anhydro-hydroxy-progesterone and estrogens to a small group of patients with functional menometrorrhagia. During 14 cycles of this therapy, the incidence of progestational endometria was 54%, whereas the incidence of these prior to therapy had been only 14%. During therapy no significant alterations in the urinary excretion of sodium pregnandiol glucuronide or of androgens were encountered. Despite the fact that some patients received as much as 160 mg. of anhydro-hydroxy-progesterone daily for 14 days, no toxic symptoms occurred.

The present study concerns an attempt to devise a schedule of orally administered cyclic sterol therapy comparable to the injectional form reported in the previous communication. The data secured in these studies are analyzed with the view of evaluating the specific endometriotropic activities of these sterols, their regulatory effects on the bleeding cycle and their ultimate corrective action on the ovarian failure responsible for estrogenic bleeding and ovarian sterility.

Rationale of Therapy

The factual and theoretical considerations which prompted the cyclic employment of sterols by the oral route of administration are identical with those presented for the injectional method of cyclic sterol therapy described in the first paper of this series. We had hoped that it would prove possible to formulate a system of oral therapy which would render unnecessary multiple injections, thereby overcoming a serious objection of the patient and physician to sterol therapy.

Therapeutic Regime

The general considerations, discussed in the first paper of this series, regarding variations in dosages and in the nature of different therapeutic schedules and the methods employed for immediate hemostasis apply similarly to the present study.

In the various therapeutic schedules only two estrogens were employed: estradiol and estriol glucuronide. This selection was made in view of the general evidence available of their oral effectiveness and because we had been convinced by personal experience of their oral activity in the doses used.

The more commonly employed therapeutic schedules are summarized. The nature of the several infrequently used schedules will be apparent from the composite clinical data presented later.

(*a*) *Estradiol followed by anhydro-hydroxy-progesterone* (*ed→pg*). Estradiol, 0.5 mg. four times daily, was given for the first 10 to 14 days following the cessation of flowing. This was followed directly by anhydro-hydroxy-progesterone, 10 mg. once to four times daily, during the latter 10 to 14 days of the cycle. Therapy was discontinued if bleeding intervened.

(*b*) *Estradiol followed by estriol glucuronide and anhydro-hydroxy-progesterone concomitantly administered* (*ed→es+pg*). Estradiol, 0.5 mg. 4 times daily, was given for the first 10 to 14 days following cessation of flowing. This was followed directly by the concomitant administration of estriol glucuronide, 480 to 960 O.U. 3 times daily, and of anhydro-hydroxy-progesterone, 5 to 30 mg. 4 times daily for the latter 10 to 14 days of the cycle. Therapy was discontinued if bleeding intervened.

(*c*) *Estriol glucuronide and anhydro-hydroxy-progesterone concomitantly administered* (*es+pg*). Estriol glucuronide, 240 to 360 O.U. 4 times daily, and anhydro-hydroxy-progesterone, 5 to 10 mg. 4 times daily, were administered conjointly during the latter 10 to 14 days of the cycle. Therapy was discontinued if bleeding intervened.

(*d*) *Anhydro-hydroxy-progesterone* (*pg*). Anhydro-hydroxy-progesterone, 10 to 30 mg. 4 times daily, was given during the latter 10 to 14 days of the cycle.

METHODS OF STUDY

The method of approach was identical with the one described in the first paper of this series. Pretreatment levels of ovarian function were determined by studies of endometrial biopsies secured within the first 12 to 18 hours of episodes of bleeding and, in a few instances, by quantitations of urinary titers of sodium pregnandiol glucuronide and of 17-ketosteroids. Immediate responses to therapy were judged by alterations in the cyclicity of bleeding, by endometrial responses at the onset of episodes of bleeding which followed cycles of therapy and, in a few instances, by quantitations of urinary titers of sodium pregnandiol glucuronide and of 17-ketosteroids. The ultimate response, after the discontinuation of therapy was judged by the regulation of bleeding and by the occurrence of progestational endometria associated with bleeding.

CLINICAL DATA

A group of 36 women, whose average age was 23.1 years, was treated by various schedules of orally administered sterols. None of these patients presented any signs of endocrine disorder except irregularity of bleeding and lowered fertility. The composite data of these patients are summarized in table 1.

Preliminary hemostasis. Sixteen patients had curettages prior to therapy. Fourteen patients had received previously cyclic sterols by injection. The remaining 7 patients had required no preliminary therapy.

Number and distribution of cycles of therapy. These 36 patients were given a total of 126 cycles of therapy, an average of 3.5 cycles per patient. The largest number of cycles of therapy per patient was 10 (in 2 instances); the smallest number was 1 (in 7 instances).

The distribution of therapeutic schedules according to kind and frequency of use was as follows.

Therapeutic Rx	Total no. of cycles	No. of cycles during which endometrial studies were made
Ed→es+pg[3]	38	28
Ed→pg	52	42
Es+pg	12	6
Pg	12	7
Es→pg	5	5
Es→es+pg	4	3
Ed→es	1	0
Ed	2	2

Dosage of anhydro-hydroxy-progesterone. A total of 68,455 mg. of anhydro-hydroxy-progesterone was given during this study. The total cyclic dosage per patient ranged from 60 to 2,080 mg. The average dosage per cycle was 556.5 mg., whereas the average dosage per cycle in which endometrial biopsies were taken was 535.9 mg. In 3 of the 126 cycles, no anhydro-hydroxy-progesterone was given. In 93, or 75.6% of the 123 cycles in which anhydro-hydroxy-progesterone was given, the cyclic doses per patient ranged from 60 to 600 mg.

Cyclicity and duration of flowing during therapy. Data in this regard are presented in figure 1. The average length of the cycle during therapy was 25.3 days. The average duration of the bleeding phase was 5.4 days.

Endometrial responses prior to therapy. The bleeding of 34 of the 36 patients occurred from estrogenic

[3] Explanations of these abbreviations are given in table 1 and in the discussion of *Therapeutic Regimes*.

TABLE 1. COMPOSITE CLINICAL DATA OF THE 36 PATIENTS TREATED BY CYCLIC STEROLS GIVEN ORALLY

Case No.	Age	Menstrual history	Endometrium at bleeding before treatment	Nature of treatment and endometrial responses associated with bleeding during therapy	Endometrium at bleeding after treatment	Follow-up data
O5	30	Mm	↓E	M(ed) *2080(es+pg) O2080(ed→es+pg)	E	OB 17 mo.
O6	24	Mm	↓E	*(ed→es) M1440(ed→es+pg) M1680(ed→es+pg) O1960(ed→es+pg)	O	OB 16 mo.
O7	17	Mm	↓E+	E800(ed→pg) E330(ed→pg) E480(ed→pg) *250(ed→pg) O360(ed→pg) E520(ed→pg)	E	OB 8 mo.
O8	18	Mm	↓E+	E560(ed→pg) O560(ed→pg)	E	OB 6 mo.
O9	22	Mm	↓E	E320(ed→pg) P180(ed→pg) O320(ed→pg)	E	OB 9 mo.
O10	17	Mm	↓E+	E280(ed→pg) M400(ed→pg) E480(pg) E660(ed→es+pg) O560(pg) E320(ed→pg) E700(ed→pg)	E	→CyG
O15	18	Mm	↓E	E560(ed→pg) P480(ed→pg) O440(ed→pg) E360(ed→pg) M400(es→pg) *420(ed→es+pg)	E	→CyG
O17	27	Mm	↓E+	E80(es+pg) O360(pg)	O	→CyG
O18	15	Mm	E	E430(ed→pg) E1060(ed→pg) E280(ed→es+pg) M390(es+pg) E600(es→es+pg) O510(ed→es+pg) E520(ed→pg) E320(ed→es+pg) E360(ed→es+pg) M560(ed→es+pg)	O	→CyG
O19	22	Mm	↓E	E300(ed→pg) M280(ed→pg) E315(ed→pg) O120(es+pg) E410(ed→es+pg) E560(ed→es+pg)	O	→CyG
O20	31	Mm	↓E+	E520(ed→pg) O480(ed→pg) *440(ed→pg)	E+	→CyG
O21	27	Mm	↓E	M120(es→es+pg) M440(es→pg)	O	OB 8 mo.
O22	17	Ol	E−	P610(ed→pg) M320(ed→pg) O200(ed→pg) M560(ed→pg)	O	OB 8 mo.
O23	24	Mm	E	M280(ed→pg) E(ed) E560(ed→pg) O360(pg) E430(ed→pg) M400(ed→pg) M800(es→pg)	O	→CyG
O31	26	Ol	E+	O360(ed→pg) O280(ed→pg) E300(ed→pg) E300(ed→pg) O360(ed→es+pg)	M	OB 5 mo.
O32	17	Mm	E	E360(ed→pg) E360(ed→pg) O280(ed→es+pg)	O	→CyG
O33	14	Mm	↓E	E400(ed→pg) E720(ed→es+pg) E560(ed→es+pg)	O	→CyG
O34	29	Mm	↓E	E560(ed→es+pg)	O	→CyG
O35	22	Ol	↓E	E400(ed→pg) O780(ed→es+pg)	E	→CyG
O36	25	Mm	E	E520(ed→pg) O320(ed→es+pg) E280(ed→es+pg M880(ed→es+pg)	O	→CyG
O38	26	Mm	↓E+	E160(ed→es+pg) O400(ed→es+pg)	E	→CyG
O40	20	Mm	E	E1120(ed→pg)	O	→CyG
IX	16	Mm	E	E60(pg) M560(ed→pg) E280(ed→pg) E1400(ed→es+pg)	O	→CyG
XI	26	Mm	E+	M540(ed→es+pg) M540(ed→es+pg) E840(ed→es+pg) M840(ed→es+pg) O840(pg) M480(es+pg) O280(es+pg) O120(es+pg) O120(es+pg) O480(es+pg)	E	OB 2 mo.
XVII	28	Ol	E	O560(pg) E780(pg)	O	OB 8 mo.
A4	38	Mm	E	E400(ed→es+pg) M320(ed→es+pg) E320(ed→es+pg)	O	OB 12 mo.
B6	19	Mm	E	E560(ed→pg) M440(es+pg) E840(ed→es+pg) E−400(ed→pg) M780(pg)	O	→CyG
B8	20	Mm	↓E	O1120(ed→es+pg) E840(pg) E420(es+pg)	O	→CyG
B10	29	Mm	E	E460(ed→es+pg) O820(ed→es+pg)	O	→CyG
B19	26	Mm	E	E540(ed→es+pg)	O	→CGP
B23	15	Mm	E	E360(ed→pg)	O	→CyG
B25	24	Mm	E	E400(ed→pg) E420(ed→es+pg) M690(es+pg)	O	→CyG
CGP1	37	Mm	E	M560(pg)	M	OB 8 mo.
CGP5	24	Mm	E	M720(ed→es+pg)	O	→CyG
B7	28	Mm	M	E280(es→pg) E280(es→es+pg) P360(es→pg)	O	→CyG
XXIII	17	Mm	M	M1400(pg)	P	OB 19 mo.

Menstrual history: Ol, oligomenorrhea; Mm, menometrorrhagia. Endometrium at bleeding before, during and after treatment: ↓ curettage prior to therapy; E, persistent estrogenic endometrium; E+, hyperestrogenic endometrium; M, mixed progestational endometrium; P, normal progestational endometrium; * biopsy, insufficient tissue obtained; O, no biopsy. Nature of treatment and associated endometrial responses: Numerals following endometrial responses indicate total cyclic dosage of anhydro-hydroxy-progesterone in mg.; the treatment formulae given in parentheses for each cycle have been explained under *Therapeutic Regime*. Follow-up data: OB, followed by number of months indicates that no further treatment has been given during the specified intervals of months; →CyG, indicates that the patient was transferred to cyclic gonadotropic therapy; →CGP, indicates that the patient was transferred to cyclic therapy with chorionic gonadotropins and progesterone.

endometria of various degrees of proliferation. In the analysis of endometrial responses to therapy, only these patients with estrogenic bleeding are considered. The pretreatment endometrial responses of these patients were distributed as follows.

Hypoestrogenic	1 patient
Persistent estrogenic	25 patients
Hyperestrogenic	8 patients

Endometrial responses during therapy. The composite data of table 1 give the individual responses of each patient. Figure 2 presents the incidence of the various endometrial patterns prior to therapy, during each cycle of therapy and after treatment was discontinued.

During 94 of the 122 cycles of therapy given the 34 patients with estrogenic bleeding, endometrial responses were sampled by biopsies. In 5 instances insufficient tissue for study was obtained; therefore, the total number of responses evaluated was 89.

The distribution of these endometrial responses

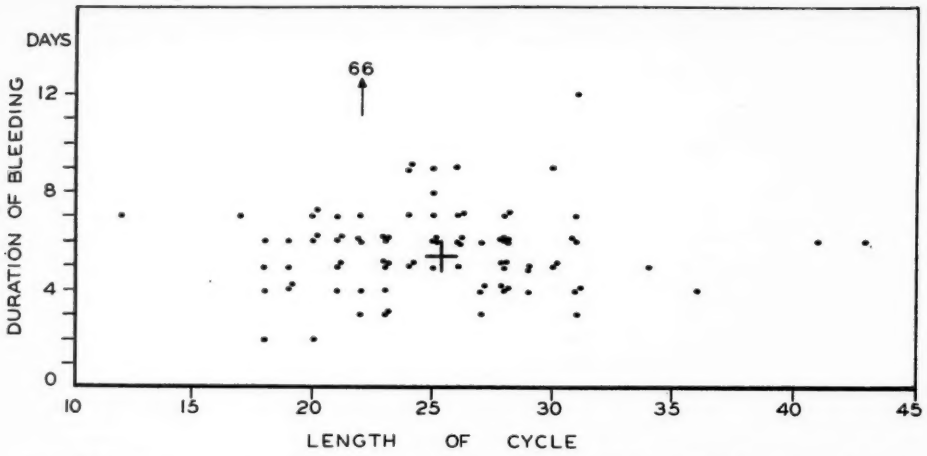

Fig. 1. The lengths of cycles and the durations of bleeding during orally administered cyclic sterol therapy.

according to kind, frequency of occurrence and percentage of incidence was as follows.

Hypoestrogenic	1 occurrence	1.12%
Persistent estrogenic	58 occurrences	65.17%
Mixed progestational	27 occurrences	33.71%
Normal progestational	3 occurrences	

Analysis of the data in table 1 indicates that 16 of the 34 patients experienced no progestational alterations during cycles of therapy (2 of these patients had given satisfactory responses to cyclic sterols by injections). The average dosage of anhydro-hydroxyprogesterone given these 16 patients was less than that given the entire group: i.e., 497 mg. and 556.5 mg., respectively. The average number of cycles of therapy was also less than that given the entire group, i.e., 2.4 and 3.5, respectively.

The other 18 patients, however, experienced progestational responses in 30 of the 65 cycles sampled, an incidence of 47.7%. (One progestational response occurred during a cycle in which no anhydro-hydroxyprogesterone was given.)

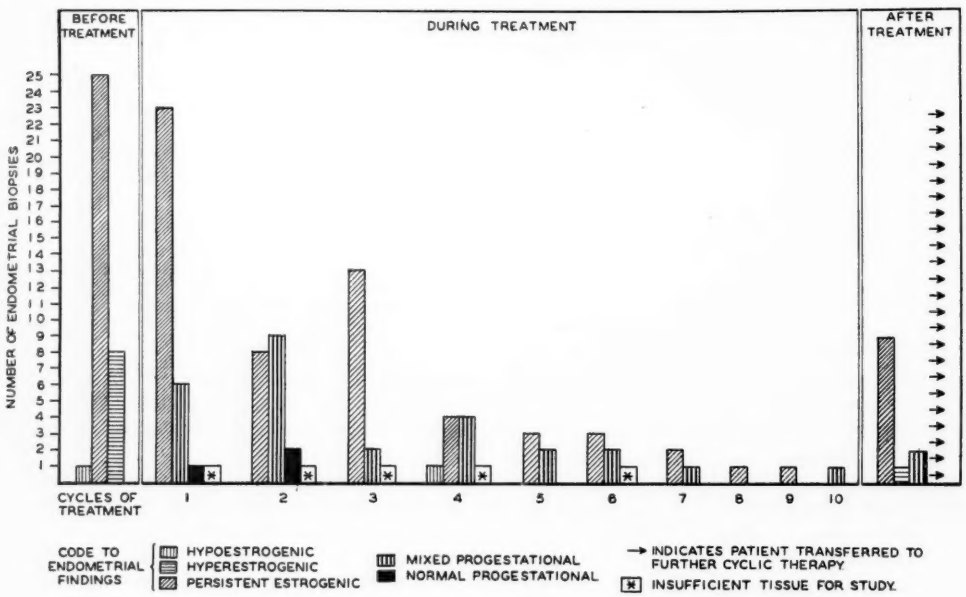

Fig. 2. Endometrial responses before, during and after orally administered cyclic sterol therapy.

The various cyclic doses of anhydro-hydroxy-progesterone which were followed by progestational responses ranged from 120 to 1,680 mg., the average cyclic dose being 597 mg. Of the various cyclic doses given 75.6% was of amounts less than 600 mg. Of the 29 progestational responses which followed therapy, 20, or 69% were associated with antecedent doses of anhydro-hydroxy-progesterone which were less than 600 mg. Of the 29 progestational responses, 9, or 31%, followed doses larger than 600 mg. These data indicate an efficiency of 26.3% for cyclic doses less than 600 mg. and one of 56.2% for doses in excess of 600 mg.

The correlations of the type of therapeutic schedule, the average dosages of anhydro-hydroxy-progesterone and the occurrence of progestational responses were as follows.

Treatment schedule	Average dose of anhydro-hydroxy progesterone	No. of cycles given during which endometrial responses were sampled	Incidence of progestational alterations	Yield of progestational responses
	mg.			%
Ed→es+pg	835.5	28	9	32.1
Ed→pg	407.0	42	10	23.8
Es+pg	487.5	6	4	66.6
Pg	670.0	6	2	33.3
Es→pg	546.6	3	3	100.0
Es→es+pg	120.0	2	1	50.0

Effects of therapy upon the urinary excretion of 17-ketosteroids and pregnandiol complex. The urinary excretion of 17-ketosteroids was investigated during 4 cycles of 4 patients prior to therapy. The average daily values for different patients ranged from 26 to 101 I.U. The average daily value for the group was 56 I.U. Similar determinations were made during 10 cycles of 4 patients under therapy. The average daily values for different patients ranged from 15 to 91 I.U. The average daily value for the group was 42 I.U.

The urinary excretion of sodium pregnandiol glucuronide was investigated during 5 cycles of 5 patients, prior to therapy. The value per cycle for different patients varied from 5 to 19 mg. The average value per cycle for the group was 10 mg. Similar determinations were made during 10 cycles of 5 patients under treatment. The value per cycle for different patients ranged from 3 to 14 mg. The average per cycle for the group was 6 mg.

Endometrial responses following discontinuation of therapy. After therapy was discontinued, biopsies were done on 12 patients at the onset of episodes of bleeding which followed cycles of no treatment: 6 of these patients had experienced progestational responses during therapy and 6 had not.

The distribution of the endometrial responses of the 12 patients investigated was as follows.

Persistent estrogenic	9 patients	83.33%
Hyperestrogenic	1 patient	
Mixed progestational	2 patients	16.66%

One of the patients, giving mixed progestational responses after therapy, had experienced similar responses during therapy; the other patient had not.

Clinical course of patients after discontinuation of therapy. The clinical course of the 16 patients who experienced no progestational alterations during therapy is summarized here.

Eleven were transferred to cyclic therapy with gonadotropins.

One received cyclic therapy with chorionic gonadotropins and progesterone.

One whose therapy stopped November, 1939, reported cyclic bleeding for 3 months thereafter.

Three whose therapy stopped November, 1939, January, 1940, and February, 1940, reported return of oligomenorrhea which characterized their menstrual histories prior to therapy. One of these patients showed a mixed progestational response on follow up.

The group of 18 patients who experienced progestational alterations during therapy may be summarized as follows.

One reported cyclic bleeding for 8 months following cessation of therapy. An irregularity developed subsequently which suggested pregnancy, but letters of inquiry to this patient have been unanswered.

Ten were transferred to cyclic therapy with gonadotropins.

One whose therapy stopped October, 1939, has made no reports.

One has completed therapy too recently for evaluation.

Two have reported cyclic bleeding for 2 and 8 months respectively following cessation of therapy in November, 1939. The follow-up biopsy of the latter of these two patients showed a mixed progestational response.

Three whose therapy ceased in February, July and November, 1939, reported returns of their oligomenorrhea which characterized their menstrual histories prior to therapy.

The follow-up data of the two patients whose endometria showed progestational responses prior to therapy are included for completeness.

One of these patients had no follow-up biopsy, being transferred directly to cyclic therapy with gonadotropins. The other, whose follow-up endometrium showed a normal progestational response, reported cyclic bleeding for 5 months following cessation of therapy in December, 1938. During two of these months of cyclic bleeding, endometria were sampled and showed mixed progestational responses.

None of these 34 patients has required recourse to curettage or roentgen therapy because of failures of conservative endocrine therapy.

DISCUSSION

The regulatory effects of this form of therapy upon uterine bleeding were not quite as satisfactory as those afforded by sterols given by injection. The continuation of cyclic bleeding after cessation of therapy was less frequent after orally administered than after injected sterols. The same tendency of patients, who had had oligomenorrhea prior to therapy, to experience this same irregularity was observed after discontinuation of either form of treatment. None of these patients has required additional therapy because of return of menometrorrhagia. Attempts to induce specific ovarian responses explain the reason for transfering a number of these patients to gonadotropic therapy.

While the data submitted indicate that a higher yield of progestational responses followed total cyclic doses of anhydro-hydroxy-progesterone which were in excess of 600 mg., the assumption is not warranted that smaller doses under more propitious conditions might not have proven quite effective. The smallest dose given for a cycle in which the endometrial responses was sampled, i.e., 120 mg., was followed by a progestational response. When the type of therapeutic schedule employed is correlated with the average total dosage of anhydro-hydroxy-progesterone, these deductions seem warranted in regard to pharmacologic efficiency: the concurrent administration of estriol glucuronide and anhydro-hydroxy-progesterone during the latter half of the cycle (es+pg) was most effective in regard to endometriotropic responses. The use of anhydro-hydroxy-progesterone alone (pg) was least effective. The preliminary use of estradiol during the first half of the cycle did not enhance the incidence of progestational responses. (These deductions do not consider data upon formulae es→pg and es→es+pg, since these were employed only for a few cycles of therapy.) Additional studies should be done in which small doses of anhydro-hydroxy-progesterone are given concurrently with estriol glucuronide.

Since no evidences of gastrointestinal, renal or hepatic toxicity were encountered from this type of therapy, even when daily doses of 160 mg. of anhydro-hydroxy-progesterone were given for 13 days, no justification exists for any fear of untoward responses to the smaller doses usually advised by the manufacturers of this compound.

The incidence of progestational responses during therapy was slightly greater when orally administered sterols were used (33.7%) than when injected sterols were given (29.2%). The same inconstancy of response, however, characterized both groups of patients.

No evidence exists from the follow-up studies of the 12 patients previously treated with orally administered sterols that any ultimate salvage was effected. Only two of these patients experienced progestational responses (an incidence of 16.7%) after therapy was concluded; it is felt that sporadic spontaneously occurring alterations in ovario-endometrial reciprocities may have well accounted for these, particularly in view of the fact that one of these patients had failed to show progestational responses during active therapy. It had been hoped that these studies would permit the formulation of a relatively economical and simple system of therapy which was as effective as that given by injection. An effective therapy, however, which required the large dosages generally employed in our therapeutic schedules, would be impossible from the standpoint of cost of the sterols.

Studies of the urinary titers of 17-ketosteroids prior to and during therapy indicate that anhydro-hydroxy-progesterone (17-ethinyl testosterone) is not metabolized similarly to testosterone, i.e., does not increase the urinary titers of 17-ketosteroids. As a matter of fact, similarly as observed in the group of patients who received injected sterols, these urinary titers decreased during therapy as a result of the depressive effects of the estrogenic portions of the therapy. Studies of the urinary titers of sodium pregnandiol glucuronide indicate that progestational responses may be induced by therapy with anhydro-hydroxy-progesterone without any increase occurring in the titers of this complex.

Difficulty is encountered in explaining the differences in the two forms of sterol therapy which are responsible for one yielding ultimate salvage and the other not doing so, despite the fact that both exerted rather similar degrees of efficiency in producing progestational responses. It may be suggested that ultimate salvage by cyclic sterol therapy has two aspects: (*a*) the correction of the endometriopathy responsible for the disturbances in sterol metabolism and endometrial responsiveness (discussed in the previous paper) and (*b*) the 'conditioning' and calibration of pituitary function with ovarian function. Both orally administered and injected sterols apparently were able to accomplish the first of these functions. Only the injected sterols were able to produce the second alteration, perhaps, due to either the greater effectiveness of the estrogens employed or of progesterone, alone or in combination with estrogens.

SUMMARY

A group of 36 young women, average age 23.1 years, with menometrorrhagia and ovarian sterility characterized by bleeding from estrogenic endometria was treated by the cyclic and oral administration of anhydro-hydroxy-progesterone and estrogens. A total of 126 cycles of therapy was given, an average

of 3.5 cycles per patient. Immediate responses to therapy were judged by the duration and cyclicity of bleeding and by specific responses of the endometria, as evidenced by biopsies taken at the onsets of episodes of bleeding. Ultimate therapeutic salvage was evaluated by continuation of cyclic bleeding, by the spontaneous recurrence of qualitatively normal ovario-endometrial cycles and by the occurrences of pregnancies after discontinuation of therapy. None of the patients treated fulfilled all these criteria. While the immediate endometrial response to therapy was good, only 16.7% of the patients investigated by endometrial biopsies after discontinuation of therapy showed spontaneous recurrences of progestational endometria. Cyclicity of bleeding did not continue as often after orally administered therapy as after injected therapy. The present data do not permit attributing any significant ultimate therapeutic salvage to orally administered sterol therapy.

We are indebted to the Schering Corporation, Bloomfield, New Jersey and to Ayerst, McKenna & Harrison, Montreal Canada for the generous amounts of sterols supplied. The former supplied anhydro-hydroxy-progesterone (pranone) and estradiol (progynon-DH); the latter supplied estriol glucuronide, as powdered sodium estriol glucuronide and as liquid emmenin.

ADDENDUM

Patient 031 who received her last treatment February, 1940, and who was reported as having been one of the two patients considered salvaged by therapy returned to the Obstetrical Division December, 1940, at which time a diagnosis of pregnancy of three months' duration was made.

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ESTROGEN, TESTOSTERONE AND GROWTH HORMONE IN THE PRODUCTION OF ATYPICAL EPITHELIAL GROWTHS IN THE HUMAN CERVICAL MUCOSA

HORMONAL PRODUCTION OF EPITHELIAL GROWTHS

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IN PREVIOUS COMMUNICATIONS (1–4) physiological effects of the ovarian hormones on the histological components of the human cervical mucosa were reported, and also observations made on the atrophic cervical mucosa of castrated women following ovarian hormonal treatment. It was shown that estrogen has a specific growth stimulating effect on the columnar epithelial elements, which can be depressed by the simultaneous administration of progesterone. Estrone and progesterone, when given simultaneously, produce a markedly increased growth in the squamous epithelium of the cervix. In all of my cases the proliferation of the two epithelial elements was found to be orderly under ovarian hormonal stimulation. When estrone is given in sufficient amounts to a castrated woman, the atrophic cervical mucosa is changed into a structure which presents the typical picture of glandular hyperplasia. The clinical and histological picture of so-called endocervicitis and erosion can be produced in dry, atrophic cervices by long-continued estrone administration. Evidently, in the production of endocervicitis and erosion there is an important hormonal etiologic factor. Since the amount of cervical discharge depends on the number of glands and their intrinsic capacity to produce mucus, for the cure of a pathologically active glandular function the hormone has to be found which is capable of counteracting the effects of estrone hyperfunction. In search for such a hormone I began experimenting with testosterone propionate. In recent years several authors have recorded their observations of changes in the histological pattern of the uterine mucosa after the administration of the male sex hormone, and indicating that glandular hyperplasia of the endometrium undergoes atrophic changes after treatment with testosterone propionate. It seems logical to expect similar changes in the cervical mucosa. In the following case of endocervicitis treated with testosterone propionate clinical and histological observations are reported.

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CASE REPORT

Case 1. A 36-year-old woman menstruated every 26 to 30 days. Until one year ago the flow was profuse for 7 to 8 days; for the past year it had been moderate in amount and lasted for 4 to 5 days. There was no history of gonorrheal infection. The patient's only complaint was profuse white discharge, which had persisted for the past 10 years. Gynecological examination revealed a normal appearing portio but there was a copious, sticky discharge from the cervical canal. The uterus was found to be moderately enlarged, firm, and freely movable. The adnexa were normal. Before hormonal treatment was begun, a cervical biopsy was taken from the anterior surface. The surface of the mucous membrane was covered with a high layer of squamous epithelium. The underlying stroma was edematous, infiltrated with round cells, and showed circumscribed infiltrates. The glands were numerous, distended, revealing papillary projections, and many of them had considerable mucus content. The lining epithelium was of high columnar type, showing signs of secretion. The capillary vessels of the edematous stroma were markedly distended, and filled with erythrocytes and polymorphonuclear leukocytes. There were several Nabothian cysts in the stroma.

This specimen represented the typical picture of a chronic endocervicitis. The patient received testosterone propionate injections twice weekly. The first week she received 50 mg., the second week 100 mg., and the third week 150 mg. By the end of the third week the patient had been given a total of 300 mg. of testosterone propionate. At this time another cervical biopsy was taken from the not yet denuded anterior surface of the endocervix. The histological findings were the following. The glands were moderate in number and were lined with epithelium which varied from high to low columnar. Most of the glands

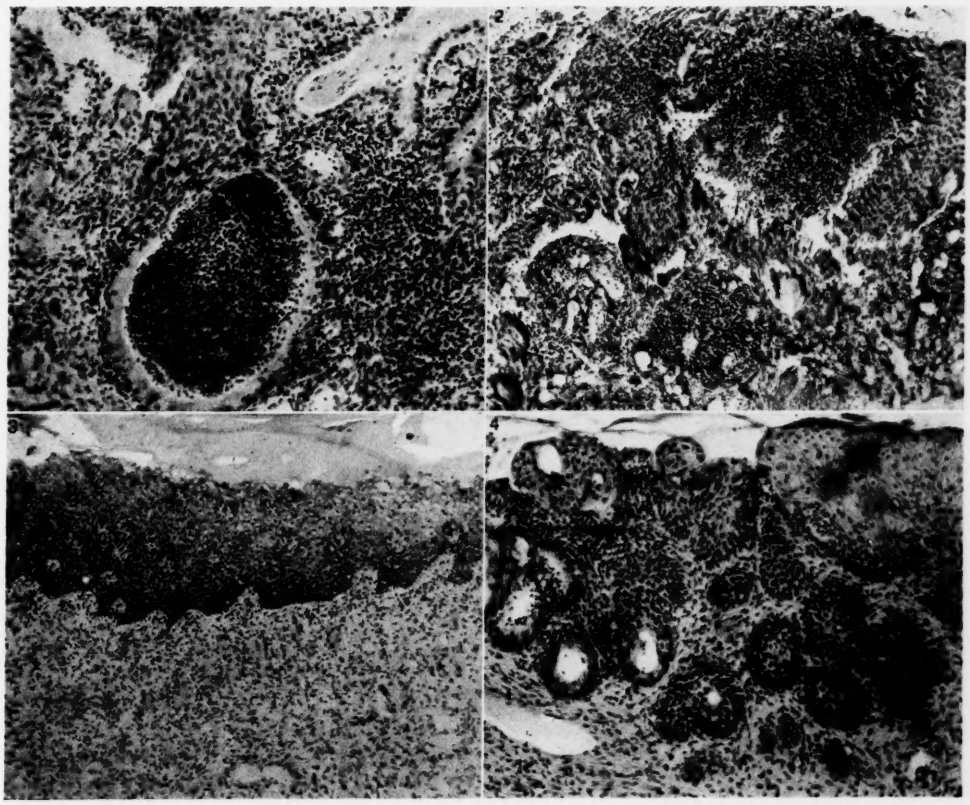

Fig. 1–4.

were regular in outline, round or oval shaped. The stroma near the surface was edematous and infiltrated with round cells. The deeper stroma was dense, the capillaries having thick walls, and some of them were markedly contracted. A large area of the surface was covered with stratified epithelium. At a place where it ceased, a deep epithelial plug was seen invading the stroma. This area is shown in figure 1. The basal layer of this plug encroached on a superficial gland, the lining epithelum of which was low columnar, and its lumen was densely filled with leukocytes. At the place where the down-growing epithelium pressed on the gland, the lining epithelium was thinned out giving the impression of an impending breaking through. There was a marked round cell infiltration around this area.

Treatment with testosterone propionate was continued the patient receiving 150 mg. in the fourth week, 200 mg. in the fifth, and the same amount in the sixth week. At the end of 6 weeks' treatment the patient had received 750 mg. Another cervical specimen was taken from the posterior surface of the cervix, and was subjected to histological study. Very few glands were found, lined with moderately high columnar and cuboidal cells. There was no sign of secretion. The stroma was a dense structure with markedly contracted blood vessels. The covering stratified epithelium near the portio was well defined, and toward the cervical canal the basal cell layer revealed deep invasions at several places. Several mitotic figures could be seen among the invading cells, the basal membrane was broken, and the invading epithelium compressed several glands, the lining epithelium of which was in the process of desquamation. The stroma near the invasion was densely infiltrated with round cells, chiefly lymphocytes. Figure 2 demonstrates a part of this area.

In this case of endocervicitis the administration of testosterone propionate produced marked histological changes. The edematous and hyperemic stroma changed into a dense anemic structure. The number of glands decreased considerably, the proliferating, highly active columnar cells being converted into a non-secreting low columnar type. The clinical symptoms corresponded with these changes. The amount of cervical discharge gradually decreased and ceased completely toward the end of the treatment. The clitoris became enlarged and the patient reported an increased libido.

The histological change in one surface area near the external os was in sharp contrast with the changes observed in the rest of the specimen. Here a marked activity of the squamous epithelial elements was noted, culminating in the course of the treatment in a histological picture which strongly resembled a beginning malignancy. The study of the periodic specimens permits a tracing of this gradual change. In

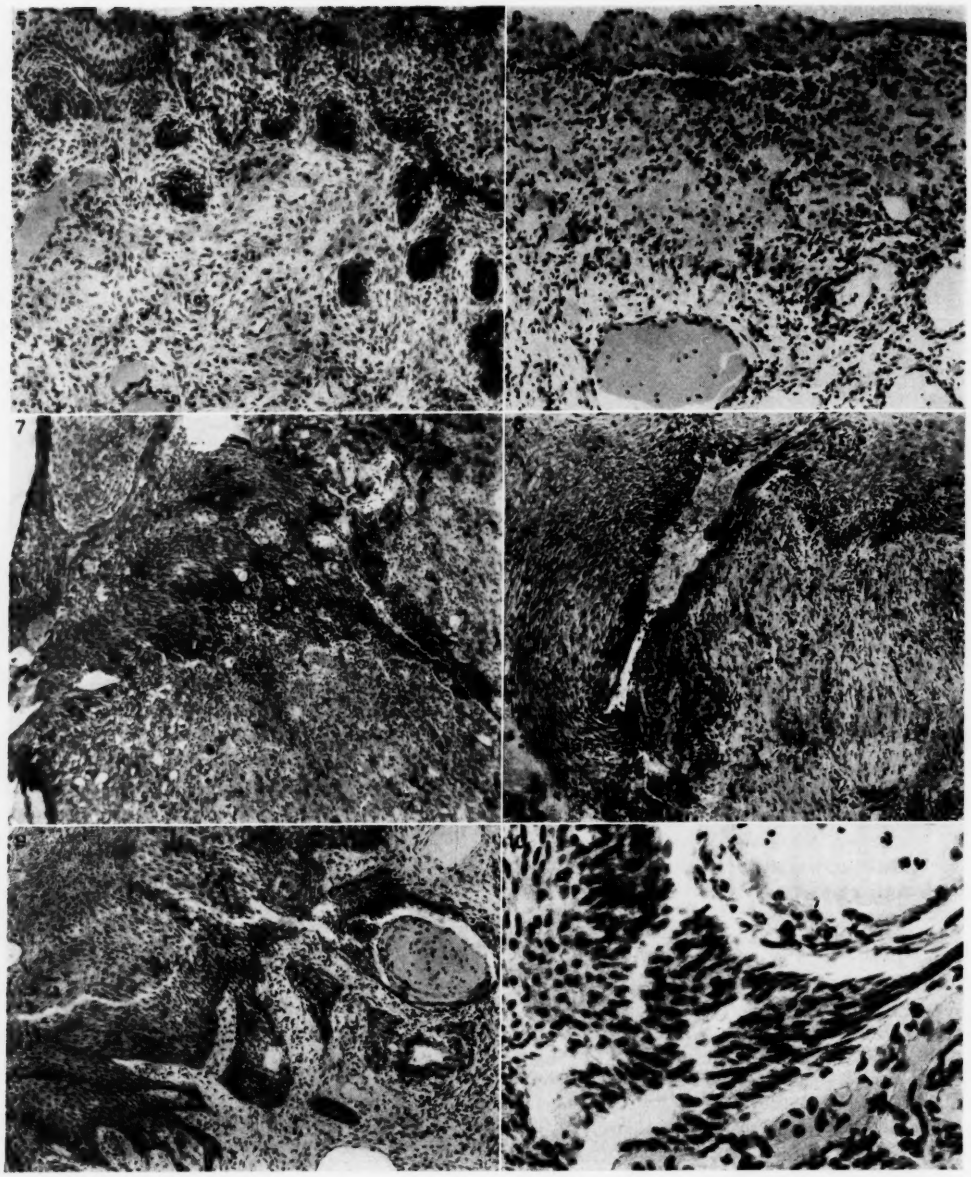

Fig. 5–10

figure 1 a marked, but regular proliferation of the squamous epithelium was seen invading the stroma and reaching and enveloping a superficial gland. The basal membrane remained intact. In figure 2 a deeper, more extensive invasion was noted, the basal membrane appeared to be broken at several places. It seems that in this case the proliferation of the squamous epithelium became gradually accelerated, changing into excessive growth in the course of the hormonal treatment.

After the observations in this case, it seemed necessary to investigate the specific histological effects of testosterone propionate on the cervical mucosa, before continuing its therapeutic application in endocervicitis. For this purpose two castrated women were selected. In each case the histological changes in the atrophic cervical mucosa after the administration of the male hormone were followed.

Case 2. A 39-year-old woman, married for 19 years, had one child 17 years ago and an abortion 10 years ago. The menstrual periods were regular with profuse flow for 3 days. Her chief complaints were severe, constant pain in

the lower abdomen, and headache. The gynecological examination revealed markedly relaxed vaginal walls and a normal appearing portio. The uterus was large, extremely retro-displaced and in the right cornu a large fibroid was palpable. The appendix was tender on palpation. A supravaginal hysterectomy with removal of the adnexa and appendectomy were performed. The patient made an uneventful recovery.

Eight weeks after the operation the patient complained of hot flushes. The gynecological examination at this time revealed a small dry portio and negative pelvic findings. A cervical specimen was taken from the anterior surface of the endocervix, before the beginning of hormonal treatment. The histological study of this specimen revealed the following. The moderate number of glands were widely scattered in the stroma and were regular in shape. Their lining epithelium was of a cuboidal type. The small nuclei which were close to the basal membrane are deeply stained. The stroma was very dense, and the capillaries were contracted. The surface of the mucous membrane was covered with a moderately high layer of squamous epithelium in the process of retrogression. The basal layer consisted of inactive cells and the basal membrane was sharply defined against the dense stroma. Figure 3 demonstrates this area.

Since the patient was ovariectomized, testosterone propionate was given with estrone, to provide the missing ovarian hormone. Injections were given twice weekly, both hormones being drawn into one syringe and injected together intramuscularly. The patient received 20,000 R.U. of estradiol benzoate and 25 mg. of testosterone propionate in each of the first and second weeks; 12,000 R.U. and 100 mg. the 3rd week; 12,000 R.U. and 150 mg. the 4th week; and 20,000 R.U. and 200 mg. in each of the 5th and 6th weeks. After 6 weeks' treatment the patient had been given 104,000 R.U. of estradiol benzoate and 700 mg. of testosterone propionate. One week after the last injection another cervical specimen was taken from the posterior surface of the cervical mucosa. The histological study of serial sections of this specimen showed the following. There was an increase in the number of the glands. The lining epithelium was of varied type. In some glands it was moderately high, in others high columnar. The stroma was dense, the capillaries were conspicuous and contracted. Marked changes were observed in the covering squamous epithelium. This area is shown in figure 4. In the area where the squamous epithelium ceases, a deep invasion of the epithelial cells into the stroma and into the superficial glands is seen. The invasion into the stroma occurred through a broken basal membrane and here the invading epithelial cells reveal marked irregularities. Different phases of the epithelial invasion into the glands can be seen in this picture. Some of the glands reveal the mechanism with which beginning invasion occurs. Here it is apparent how the invasion takes place along the basal membrane of the glands, whereby the original lining epithelium is being rolled off and gradually displaced toward the lumen of the glands. Due to the proliferative activity of the invading epithelium some glands were entirely filled with epithelial cells, giving the impression of well demarcated epithelial islands in the stroma. Inflammatory cells accompanied the invasion around and within the glands.

Case 3. A 46-year-old woman, married for 16 years was never pregnant. Menstrual periods were normal. The patient's chief complaint was pressure and pain in the lower abdomen. Gynecological examination revealed a normal appearing, small portio, the uterus was large, and several fibroid tumors were palpable. A supravaginal hysterectomy with removal of the adnexa was performed.

Seven weeks after the operation examination revealed a small, dry portio. Before beginning of hormonal treatment, a cervical specimen was taken from the anterior surface of the endocervix. The histological study of this specimen revealed an inactive, atrophic structure. Simultaneous administration of estrone and testosterone propionate was begun and given as described in the previous case. The patient received, in the course of 6 weeks' treatment all together 96,000 R.U. of estradiol benzoate and 750 mg. of testosterone propionate. One week after the last injection another cervical specimen was taken from the posterior surface of the cervical mucosa. The histological study of serial sections of this specimen revealed similar changes to those observed in the previous case. Squamous epithelial elements were seen invading the glands, and several well demarcated epithelial islands were found deep in the stroma. Figure 5 illustrates an area of this specimen.

In two castrated women the simultaneous administration of estrone and testosterone propionate produced atypical epithelial proliferations in an atrophic cervical mucosa. In animal experimentation, Korenchevsky and Hall (5) reported the production of gigantic uteri after the simultaneous administration of estrone and testosterone propionate. The hypertrophy was caused by increase in the number and size of the cells. They also observed in these cases a most severe degree of squamous metaplasia which they consider as the first stage of precancerous changes. Recently, Gardner (6) has completed a series of injections in mice in which male hormone was injected simultaneously with estrogen. The incidence of cervical carcinoma in these mice was higher than in the series in which estrogen alone was used.

It is believed that testosterone propionate combines the actions of estrone and progesterone. This property is not likely to be of importance as far as the production of atypical epithelial growths is concerned. In several castrated women, the histological effects on the atrophic cervical mucosa after simultaneous administration of estrone and progesterone were followed. While a marked squamous epithelial proliferation in these cases was observed, up to the present time I have not been able to duplicate the histological changes reported above. Evidently, testosterone propionate when acting together with estrone has a specific growth stimulating effect on the squamous epithelium of the human cervical mucosa. Hofbauer (7, 8) by injecting extracts of the anterior pituitary lobe, or transplanting the gland intramuscularly into guinea pigs, was able to demonstrate histological changes in these animals which resemble the pictures obtained in my experimental study. This similarity of results intimates that testosterone pro-

pionate with estrone may produce atypical epithelial proliferations through their influence on the anterior pituitary. To determine what histological effects the anterior pituitary hormones have on the human cervical mucosa, extensive studies were carried out in the course of which it was found that the growth hormone of the anterior pituitary lobe when acting together with the ovarian hormones exerts a marked stimulating effect on the epithelial growth. These observations are reported in the following.

Case 4. A 47-year-old woman had been married for 27 years, and had two children. She underwent a supravaginal hysterectomy with removal of the adnexa, for multiple fibroids. Two years after the operation the patient was still suffering from hot flushes. The vaginal examination revealed a small, dry portio, and the pelvis was negative. A cervical specimen was taken, the histological study of which revealed a characteristic atrophic picture. Figure 6 shows a portion of the specimen. The surface was covered with an atrophic squamous epithelium, the basal layer consisted of a single row of inactive cells, and the basal membrane formed a straight line which is sharply demarcated. Estradiol benzoate was given in the form of progynon-B, and progesterone in the form of proluton. As the growth hormone the Parke, Davis preparation known as antuitrin growth, which contains 10 rat growth units in each cubic centimeter, was administered. The patient received injections twice a week. All of the hormones to be administered were drawn into one syringe and were injected together intramuscularly. The first week 6000 R.U. of estradiol benzoate and 2 mg. of progesterone were given; the second week 14,000 R.U. and 6 mg.; third week 20,000 R.U. of estradiol benzoate; 10 mg. of progesterone and 20 R.U. of growth hormone; fourth week 20,000 R.U., 10 mg. and 40 R.U.; fifth week 20,000 R.U., 15 mg. and 20 R.U.; sixth week 10,000 R.U. of estradiol benzoate and 15 mg. of progesterone. In 6 weeks' treatment the patient was given a total of 90,000 R.U. of estradiol benzoate, 58 mg. of progesterone and 80 R.U. of growth hormone.

One week after the last injection another cervical specimen was taken from the not yet denuded surface of the endocervix. Figure 7 demonstrates an area of this specimen. A very marked, irregular activity of the squamous epithelial elements can be seen. In the upper layers the histological picture of parakeratosis is present. There is a tremendous proliferation in the basal layers, which break through the basal membrane and invade the stroma. The invading epithelium is surrounded by a round cell infiltration. A marked hyperemia is seen. Similar epithelial changes were found in several other areas of the specimen.

Case 5. A 42-year-old woman, married for 10 years, was never pregnant. She underwent a supravaginal hysterectomy with removal of the adnexa, for multiple fibroids. Ten weeks after the operation gynecological examination revealed a small, atrophic portio, and the pelvic findings were negative. A cervical biopsy taken at this time showed an inactive cervical mucosa. Hormonal treatment was begun according to the plan described in the previous case. The patient received in 7 weeks' treatment all together 96,000 R.U. of estradiol benzoate, 45 mg. of progesterone and 60 R.U. of growth hormone. One week after the last injection another cervical specimen was taken, and studied on serial sections. An excessive, invasive squamous epithelial growth could be seen in several areas of the specimen. Figure 8 shows one of these areas.

In two castrated women the combined action of the ovarian hormones with the growth hormone of the anterior pituitary produced atypical epithelial proliferations in the atrophic cervical mucosa. Such excessive proliferations were not observed in cases which were treated with estrone and progesterone alone. It must be assumed, therefore, that the growth hormone is capable of giving the added stimulation which changes a normal proliferation into an excessive, invading growth. Finally, histological observations in an atrophic cervical mucosa of a castrated woman, who received estrone, testosterone propionate and small doses of growth hormone, are reported here.

Case 6. A 29-year-old woman underwent a supravaginal hysterectomy with removal of the ovaries, for a large fibroid. Seven weeks after the operation hormonal treatment was begun. The first week the patient received 20,000 R.U. of estradiol benzoate and 25 mg. of testosterone propionate; 2nd week 20,000 R.U. and 75 mg.; 3rd week 12,000 R.U. and 125 mg.; 4th week 12,000 R.U. and 175 mg.; 5th week 12,000 R.U. and 200 mg.; 6th week 4,000 R.U. of estradiol benzoate, 75 mg. of testosterone propionate and 40 R.U. of growth hormone; 7th week 4,000 R.U., 75 mg., and 40 R.U.; and the 8th week 40 R.U. of growth hormone. In 8 weeks' treatment the patient received all together 84,000 R.U. of estradiol benzoate, 750 mg. of testosterone propionate and 120 R.U. of growth hormone.

One week after the last injection a cervical specimen was taken for histological study. The findings were the following. The surface was covered with regularly arranged layers of stratified epithelium. Abruptly the basal layers showed deep projections into the stroma. There were places where the connection between basal layer and islands of epithelium was lost. Individual epithelial nests could be observed deep in the stroma, apparently filling out lymph spaces. Close to the surface the wall of a cervical gland was invaded, the basal membrane of which seemed to be destroyed. Here the invading epithelial cells showed irregular mitoses and large hyperchromatic nuclei. The gland was filled with polymorph-leukocytes. There are areas in which the epithelial invasion showed narrow, long strands, suggesting the filling out of fine lymph vessels in the stroma. There was a round cell infiltration around the invading epithelia. These histological changes are shown in figure 9. An area of the invading epithelium is shown under high power in figure 10, revealing the irregularity of the cells and several multinuclear giant cells.

In this case, although approximately the same dosage of estrone and testosterone propionate was given as in *case 2* and 3 a much more advanced epithelial growth process was found. This apparently was due to the added action of the growth hormone.

For the proper interpretation of the histological pictures demonstrated in this presentation, two facts

have to be considered. First, that the changes were produced in the atrophic, inactive cervical mucosa of castrated women after a short period of treatment with relatively moderate amount of hormones. It is logical to assume that a more prolonged treatment with these hormones would have produced a progressive growth process. Secondly, that in the cases utilized for this study, inflammatory conditions in the cervical mucosa were ruled out before beginning the hormonal treatment, and that the patients refrained from sexual activity while they were under observation.

DISCUSSION

Epithelial growth process in the human cervical mucosa is an endocrine problem. The normal, cyclic proliferation of the epithelia is governed by the ovarian hormones. An imbalanced ovarian hormonal action produces an imbalanced growth of the epithelia, without attaining, however, atypical properties. The cessation of the ovarian function, on the other hand, brings about inactivity and retrogressive changes in the cervical epithelia. In the present study it was observed that testosterone propionate when acting together with estrone, or when the growth hormone of the anterior pituitary gland is added to the ovarian hormonal action, atypical epithelial proliferations can be produced in the atrophic cervical mucosa of castrated women.

Similar histological pictures to those produced in the present series are being generally interpreted as a healing phase in erosions. The theory is that the squamous epithelium growing back to the denuded surface, in its proliferation surrounds and invades the ducts of the glands. In this process some glands may be filled out entirely with squamous epithelial cells. In all of the cases reported in the present study erosions were ruled out clinically and histologically, and the development of atypical epithelial proliferations was observed following hormonal treatment.

The exact histological significance of atypical epithelial proliferations produced by the administration of hormones can not be determined at the present time. Data are accumulating in the literature which indicate that these changes may form the basis on which carcinoma develops. Boehmig (9), studying carcinoma on serial sections, believes that malignancy is primarily an orderly growth process. According to his observations specific cancerous attributes do not exist, the malignancy may be reduced to quantitative measures to an intensity or increased tempo of growth. Oertel (10) is of similar opinion. Hinselmann (11, 12) ascertained on serial sections that metaplasia changes into leukoplakia and leukoplakia into true carcinoma. Wespi (13) studied 9 early cervical carcinoma cases on serial sections, and found atypical epithelial proliferations and true carcinoma side by side. In two previously reported early cervical carcinoma cases similar observations were made (14). The role of the hormones in producing atypical epithelial proliferations, and their possible relationship to malignancy deserves further studies. In carrying out such an investigation it is essential that the specimens be studied in serial sections since the characteristic changes are likely to be confined to a few slides only.

From a clinical viewpoint, the results of the present experimental study warrant a warning against the indiscriminate use of hormones for therapeutic purposes. The histological effects of the administered sex hormones should not be judged exclusively by the endometrial and vaginal changes. It is well to remember that any sex hormone given to a human being affects the entire genital tract, and indirectly the entire endocrine system. It seems that the delicately balanced epithelia of the cervical mucosa are especially susceptible to hormonal action.

SUMMARY

In a case of chronic endocervicitis testosterone propionate was administered for therapeutic purposes. Periodic histological studies of the cervical specimens disclosed a marked decrease and inactivity of the glandular elements in the course of the treatment. In a small area, however, near the external os a marked atypical epithelial proliferation developed, which suggested a beginning malignancy. On the basis of this observation experimental studies were carried out in castrated women. In two cases the simultaneous administration of estrone and testosterone propionate produced atypical epithelial proliferations in the atrophic cervical mucosa, and in another two cases the administration of estrone, progesterone and the growth hormone of the anterior pituitary produced similar histological changes. In the sixth case estrone, testosterone propionate and growth hormone were given, and it was observed that the addition of the growth hormone accelerated the epithelial growth.

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A SURVEY OF THE USE OF THIS TEST IN ENDOCRINE INVESTIGATION, DIAGNOSIS, AND THERAPY[1]

COLORIMETRIC ASSAY OF 17-KETOSTEROIDS IN URINE

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As pointed out by Callow (1) biological assays for urinary androgenic and estrogenic steroids are specific neither for any one substance nor for the steroids originating from a single gland. There is a chemical test for steroids, however, sufficiently promising to warrant a survey of its biological and clinical significance. This is the color reaction introduced by Zimmermann (2, 3) as a test for 'androgens,' which has been further developed by Wu and Chou (4) and by Callow, Callow, and Emmens (5) for application to urinary extracts, and shown by the latter to parallel, at least roughly, the biological assay. These authors state: "In spite of the series of assumptions which must be made in attributing significance to the results of colorimetric assay the advantages of this method over the biological method are very great with respect to ease of operation, sensitivity, high reproducibility and low error." The present paper is based on the results of over 1500 such urinary assays in a study of a selected group of patients from the Massachusetts General Hospital.

TERMINOLOGY AND CHEMICAL NATURE OF SUBSTANCES MEASURED

The terminology requires a little care. The reaction is based on the fact that substances containing the grouping $-CH_2 \cdot CO-$ (i.e., an active methylene group) in the presence of alkali and meta-dinitrobenzene produce a red color which may be used for quantitative assay. Moreover, among the ketosteroids the color produced depends upon the position of the ketone group. Callow, Callow and Emmens (5) showed that steroids with a ketone group on the 17th carbon atom (17-ketosteroids) develop an intense broad absorption band with a maximum in the green, whereas this was not true of 3-, 6- and 20- ketosteroids. These authors used the term, 17-ketosteroids, for the designation of the substances measured by the test. This terminology has been followed in this laboratory. Estrone, which is a 17-ketosteroid (17-KS) is not included in the assay since, being a weak phenol, it is removed by washing with alkali, a step in the extraction procedure.

The terminology as regards the Zimmermann reaction is complicated by the fact that Zimmermann employed aqueous alkali whereas the later workers employed alcoholic potash and excluded all water from the reaction during the period of color development. This modification of the Zimmermann reaction increases not only the specific color but also certain non-specific colors.

It should be emphasized, furthermore, that the test is not for androgens as such, although it may parallel the biological test for the latter in many instances (vide supra). For example, aetiocholan-17one-3α-ol, is a 17-KS but not an androgen, while testosterone is an androgen but not a 17-KS. As will appear below, it would seem that the test is an index (probably not a measure) of the combined activity of the adrenal cortex and the male gonads, and that in the female, therefore, it is an index to the activity of the adrenal cortex alone.

Table 1 shows a list of the non-phenolic 17-ketosteroids which have already been identified in urine. The first two on the list can be formed by the body

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TABLE I. THE NON-PHENOLIC 17-KETOSTEROIDS WHICH HAVE BEEN FOUND IN HUMAN URINE

Chemical name	Biological name	Where found	Androgenic activity. Number of I.C.U.'s[1] in 1 mg.
1. Androstan-17-one 3α-ol	Androsterone	Normal male and female urine	10 (7)[2]
2. Aetiocholan-17-one 3α-ol	—	Normal male and female urine	0 (8)
3. Δ5Androsten-17-one 3-β-ol	Dehydroisoandrosterone (=*Trans*dehydroandrosterone)	Normal male and female urine (also large amount from adrenal tumor urine)	3.3–5.0 (7)
4. Δ3;5 Androstadein-17-one	—	Adrenal tumor urine only	2.5–2.8 (9)
5. Androstan-17-one-3β-ol	Isoandrosterone	Adrenal hyperplasia urine only	1.6–2.0 (7)

[1] International capon unit (I.C.U.) is the biological equivalent to 100γ of androsterone, the international androgenic unit.
[2] Number in parentheses indicates reference.

from testosterone (1); the third, which is the only other normal 17-ketosteroid yet identified, cannot be formed from testosterone (1) but has been found in large amounts in cases of adrenal cortical tumor (6).

METHODS USED

Collection of urine samples. For most patients 16-hour night collections (4 P.M.–8 A.M.) were made since this practice enabled outpatients to make an adequate and accurate collection. In the later tests the accuracy of collection was checked by creatinine estimations. All results are expressed as mg. of sterone (as androsterone) per 24 hours. A few observations of the day and night excretions support our assumption that the amount excreted does not vary significantly in different parts of the 24 hours.

Preservation and storage. It has frequently been claimed that these steroids decrease if the urine is allowed to stand at room temperature, especially if ammoniacal decomposition occurs (5). Each sample was collected into a bottle containing 10 cc. conc. HCl, placed in an ice box, and for the earlier tests extracted within two days. Subsequent results indicated that acidified samples might be kept in an ice box for at least a few weeks before extraction (vide infra). For many of the later estimations advantage was taken of this finding. Toluene and chloroform should not be used as preservatives, and rubber stoppers should be avoided (10).

Hydrolysis, extraction and purification. A combined hydrolysis and extraction method since published by Callow, Callow, Emmens and Stroud (8) was used together with their method of purification. The only modification employed was the use of carbon (Norrit A) for decolorization; this practice has now been abandoned (vide infra).

Colorimetric assay. For this we have followed precisely the directions given by Callow et al. (5) with the exception that the reactive mixture was diluted to 20 instead of 10 cc. before reading, and the readings were converted into mg. by a different system of calculation (vide infra). The photoelectric colorimeter used was a Summerson (11) two-cell instrument with a Leeds and Northrup box type galvanometer, with enclosed lamp and scale, of sensitivity of 0.019 amp. per mm. for balancing the potentiometric circuit. This galvanometer was altered by removing the damper winding and permitting the resistance of the photoelectric cells to serve as a damping resistance. It was found necessary to make this change because of the high resistance of the cells which greatly overdamped the instrument. Other changes made in the apparatus were as follows. General Electric photovoltaic cells were substituted for the cells in the original instrument. This alteration made it necessary to change to 450 ohms the shunting resistance across the cell receiving light coming through the test solution. The potentiometric circuit was connected to the galvanometer terminals through a Leeds and Northrup high-resistance, double pole, double throw switch. Because of the colored blank obtained in the more sensitive Callow modification of the Zimmermann reaction, it is desirable to use a two-cell photoelectric colorimeter which measures intensities in terms of ratio, rather than a one-cell instrument such as the Evelyn or the 'photolometer' which measures absolute differences in intensity. This makes the correction suggested below easier to apply.

Glass filters with the following characteristics were used. The green filter, made by the Rubicon Company, had a maximal transmission at 5120 Å. At this wave length it transmitted 11.5% of the light passing through it. At 5070 and 5190 Å it transmitted 10%, at 5010 and 5320 Å, 5%, and at 4930 and 5650 Å, 0% of the light passing through it. The violet filter, made by the Klett Company, transmitted at 4050 Å, 32% (maximal) of the light passing through it, at 4320 Å, 20%, at 4470 Å, 10%, and at 4750 Å, 0%.

Except in the earlier results we have made readings with both these filters. The green filter is specific for the steroids; the purpose of the violet filter is to obtain a reading by which a partial correction can be made for the color produced by non-specific substances. The formula finally used for this correction is a simplification of that worked out by Gibson and Evelyn (12) for a similar problem. Reactions with extracts containing no steroid were used to find the ratio (K_i) of the reading given by impurities on the violet filter to that on the green filter. A similar ratio (K_s) was found for reactions made with pure sterone. Then if G represents the reading of an unknown made with the green filter and V that with the violet, the Gibson and Evelyn formula may be used as follows.

$$\frac{K_i\,(G) - V}{K_i - K_s} = \text{Corrected reading.}$$

Actually the denominator in our specific problem is so nearly unity that it was disregarded. The colorimeter is equipped with a logarithmic scale; otherwise, the formula would require the logarithms of the readings. Another correction formula was used for some of the data but the difference in the results was usually small.

TABLE 2. EFFECT ON 17-KS ASSAYS OF STORAGE OF URINE IN ICEBOX WITH 10% HCl

Case and date of sample collections	Result of assay on first extraction	Result of assay on 2nd extraction	Change in assay after period of storage
	mg. sterone/ 24 hr.	*mg. sterone/ 24 hr.*	*mg. sterone/ 24 hr.*
1. P.S. July 2–3	7.7 (1)[1]	8.8 (14)[2]	+1.1 (14)[3]
2. A.S. April 19–20	9.0 (1)	9.6 (21)	+0.6 (21)
3. R.BI. Dec. 9–10	14.2 (1)	15.8 (8)	+1.6 (8)
4. R.BI. July 28–29	7.8 (1)	9.9 (63)	+2.1 (63)
5. A.S. July 23	9.0 (2)[2]	8.4 (161)	−0.6 (159)
6. R.Be. Sept. 15–16	3.6 (2)	3.0 (10)	−0.6 (8)
7. A.L. Oct. 12	5.4 (2)	6.6 (32)	+1.2 (30)
8. R.Be. Sept. 29–30	8.5 (4)	8.5 (32)	0.0 (28)
9. R.W. Aug. 18–19	4.3 (5)	5.7 (37)	+1.4 (32)
10. W.S. Sept. 8–9	3.9 (7)	4.0 (22)	+0.1 (15)
11. B.V. Feb. 3–4	6.5 (62)	6.2 (234)	−0.3 (172)

[1] Immediate assay.
[2] Number in parentheses indicate numbers of days after collection that extraction was made.
[3] Numbers in parentheses indicate number of days of storage between assays.

Assays were usually made within a few days, although the estimations did not vary significantly over considerable periods of storage in the icebox. Each time 12 to 16 tubes were set up including two blanks and duplicates of each extract, and all readings were converted into 'mg. of sterone' from standard curves that had been constructed from reactions with solutions of pure androsterone.

Studies on the Reliability of the Method

Storage. Table 2 shows in 11 different samples the results of storage of urine for periods varying from 8 to 172 days. Since results are reproducible only to within 1 mg. per assay, it will be seen that the differences are only slightly beyond the limits of accuracy of the procedure.

Recovery experiments. The results of recovery experiments in which pure androsterone, dehydroisoandrosterone, or androsterone benzoate was added to pooled urine are given in table 3. Urine which had been found negative for 17-KS was used except in part C, table 3. The content of the sterone solutions added was checked by colorimetric assay. The average recovery was 88%.

Recovery experiments were also carried out in order to estimate how much of this loss was due to the use of carbon. This was variable, but accounted on the average for about half. Since the data here presented were collected, the use of carbon has been omitted.

RESULTS

Degree of Day to Day Variation in 17-KS Excretion in the Same Patient Independent of Recognizable Clinical Changes

Comparisons of assays on several samples collected within a short period of time[3] from 98 patients, selected because their collections were considered accurate, showed agreement within 1 mg. in 49%, within 2 mg. in 84%, and within 5 mg. in 95% of the cases. In table 4 are shown the day to day variations in a group of students and technicians; they are of about the same order of magnitude. Chou and Wang (13) have also reported finding only slight daily variations in 17-KS excretion.

[3] Studies now in progress indicate that normal individuals, if studied for a longer period of time, may show fluctuations of about 5 mg. without any demonstrable clinical change.

Range of Normal Values

Despite these indications of a relatively constant level of excretion for each person, the excretion levels found in normal individuals cover a relatively wide range. In table 5 are shown results in healthy adults between the ages of 20 to 40. The range for males

TABLE 3. RECOVERY OF ADDED STERONE

A. Addition of pure androsterone to negative urine.

Mg. added	Mg. recovered in first 2 hr.	Mg. recovered in remaining 5 hr.	Loss, mg.	% recovery
0.0	0.0	0.0	0.00	—
1.65	1.7	0.0	−0.05	103
4.85	4.7	0.0	0.15	97
4.95	4.7	0.0	0.25	95
4.95	4.2	0.0	0.75	85
9.90	8.8	0.0	1.10	89
14.85	13.4	0.0	0.95	94

B. Addition of androsterone benzoate to negative urine.

Mg. added	Mg. recovered in 1st 2 hr.	Mg. recovered in 2nd 2 hr.	Mg. recovered in 3rd 2 hr.	Loss, mg.	% recovery
3.3	3.3	0.00	0.00	0.00	100
9.9	7.0	0.55	0.35	2.00	80
9.9	6.2	3.70	0.00	0.00	100
9.9	7.2	2.50	0.00	0.20	98
19.8	13.5	5.45	—	0.85	91

C. Addition of androsterone benzoate to urine containing some steroid.

Mg. added	Mg. recovered	Loss, mg.	% recovery
0.00	6.1	—	—
4.37	9.5	0.97	78
4.37	9.5	0.97	78
0.00	5.9	—	—
4.37	9.5	0.77	82
4.37	8.6	1.47	66

D. Addition of dehydroisoandrosterone to negative urine.

Mg. added	Mg. recovered	Loss, mg.	% recovery
0.00	0.0	0.00	—
2.55	2.3	0.25	88
4.59	4.0	0.59	85
6.10	5.8	0.30	93
9.20	8.4	0.80	89

TABLE 4. DAY TO DAY VARIATION IN 17-KS EXCRETION OF SEVEN NORMAL INDIVIDUALS

Case and Sex	Mon.	Tues.	Wed.	Thurs.	Fri.
	mg. sterone/ 24 hr.	mg. sterone/ 24 hr.	mg. sterone/ 24 hr.	mg. sterone/ 24 hr.	mg. sterone/ 24 hr.
1 ♀	11.3	8.8	—	—	—
2 ♀	7.1	6.5	7.4	—	—
3 ♀	11.0	10.5	8.7	—	—
4 ♂	9.4	—	10.4	—	11.2
5 ♂	18.3	16.4	17.9	—	—
6 ♂	16.4	13.5	14.4	—	—
7 ♂	21.7	21.3	—	24.8	—

was 8.1 to 22.6 mg./24 hr. with an average of 13.8 mg./24 hr., and for females 5.1 to 14.2 mg./24 hr. with an average of 9.0 mg./24 hr. These values correspond fairly closely with those (5.9 to 18.8 mg./24 hr.) reported by Chou and Wang (13). The range of normal values established by Callow et al. (8) is also similar except that it extends a little lower; but his cases were hospital patients and included some whose condition might have influenced 17-KS excretion. When such cases are eliminated his range of values is 6.0 to 15.0 mg./24 hr. for the males and 6.9 to 12.6 mg./24 hr. for the females.

There have already been several reports of 17-KS excretion in children (14, 15) which indicate, in general, that these are quite low until puberty, following which in a relatively few years adult figures are attained. A less complete study of the excretion in elderly persons suggests that the values fall off in the later decades. Thus, in 5 healthy elderly men studied, we obtained these values: *case A*, age 71, 3.0 and 4.2 mg.; *case B*, age 72, 2.2 and 3.4 mg.; *case C*, age 73, 4.8 and 3.7 mg.; *case D*, age 73, 4.2 and 4.1 mg.; and *case E*, age 75, 1.8 and 2.4 mg./24 hr. In a few elderly women similar findings were present.

Hamblen (16) reported that brunettes excrete more 17-KS than blondes. Fluctuations have not been found to correlate to any degree with the menstrual cycle (17); such was our experience in one case. We have made only superficial observations on the relation between the 17-KS output and race, complexion, weight, surface area and creatinine excretion, but as yet have found no striking correlation. It is to be hoped that some criteria will be found by which the normal range can be more narrowly defined.

Results in Disease

Almost all of our patients were adults; none were included in whom the diagnosis had not been made clear by other methods. The individuals studied are divided into 14 groups, the first 3 of which are non-endocrine. Abstracts of representative histories are presented in a table for each group.

1. *Malnutrition* (table 6). Since one of the more important uses of the 17-KS assay is in the diagnosis of Simmonds' cachexia (vide infra), it is of interest to know what the findings are in other wasting conditions. By and large, malnutrition due to any cause is apt to be associated with a low assay; this includes anorexia nervosa. It should be noted, however, that in a few cases of anorexia nervosa, the assays were quite normal in spite of the debility. Among the malnutrition cases those with impaired intestinal absorption had the lowest values. Cases *I* and *II* are of interest since their assays rose after successful therapy from 1.7 and 2.9 to 4.5 and 5.8 mg. per 24 hr. and from 1.8 and 1.8 to 6.6 and 4.6 mg. per 24 hr. respectively (see also *case 10*). In only one instance (*case 10*) was the assay less than 0.5 mg. for 24 hr. This was a patient with chronic terminal ileitis, steatorrhea, and deficiencies of many if not all of the fat-soluble vitamins. This failure of 17-KS to disappear entirely in most cases of malnutrition is very important since, as will appear below, the assay is almost invariably virtually zero (i.e., below 0.5 mg. per 24 hr.) in Simmonds' cachexia.

2. *Debility from other causes* (table 7). Our data are too meager on the effect of non-specific trauma on the 17-KS excretion. We had thought that we had good evidence that surgical operation itself decreased

TABLE 5. 17-KS VALUES OF 23 NORMAL INDIVIDUALS

Females	No. of samples	Average mg. sterone/24 hr.
1	10	10.6
2	3	5.5
3	1	9.9
4	1	14.2
5	2	5.1
6	2	8.4
7	1	6.6
8	1	9.0
9	2	8.2
10	1	12.8
11	2	9.0
12	3	10.1
13	3	10.1
14	3	7.0
Total	35	9.0
Range: 5.1 to 14.2 mg./24 hr.		

Males	No. of Samples	Average mg. sterone/24 hr.
1	1	13.8
2	4	14.6
3	2	8.7
4	2	11.1
5	3	22.6
6	3	17.5
7	3	14.8
8	3	12.6
9	2	8.1
Total	23	13.8
Range: 8.1 to 22.6 mg./24 hr.		

TABLE 6. ELEVEN CASES OF MALNUTRITION INCLUDING ANOREXIA NERVOSA, ULCERATIVE COLITIS, SPRUE

Case No. and hospital No.	Diagnosis	Clinical data	Number of assays	Range, mg./24 hr.	Average, mg./24 hr
1 (243322)	Anorexia nervosa	Female, 20 yr.; 93 lb.; amenorrhea 9 mo.; loss of appetite 6 mo.; nervousness, anxiety, irritability 3 mo.; loss of 25 lb. in 6 mo.; B.P. 140/40; FSH[1] negative; I.T.T.[2] showed hypoglycemia unresponsiveness. Improved markedly with treatment and 17-KS rose to 4.5 and 5.8 mg./24 hr.	2	1.7, 2.9	2.3
2 (622431)	Malnutrition; ?anorexia nervosa; amenorrhea	Female, 23 yr.; followed in the Psychiatric Department for 5 yr. since a "nervous breakdown." At that time she had lost weight from 105 to 72 lb. and menses had ceased. P.E. always negative except for malnutrition.	1	—	2.7
3 (254939)	Anorexia nervosa	Female, 20 yr.; ill 8 yr.; recurrent nausea, vomiting, and left flank pain; uterine suspension 7 yr. ago; removal of ovarian cyst 6 yr. ago; appendectomy 2 yr. ago; tonsils and adenoids removed 1 mo. ago; dyspareunia 5 yr.; diet poor in protein, butter and sugar for 2 yr.; loss of 10 lb., present weight 84 lb.; oligomenorrhea with episodes of lightheadedness, ankle edema, and frontal headache; right flank tender; 1 of 2 FSH tests positive; I.T.T. showed hypoglycemia unresponsiveness; anemia; leukopenia; purpura (serum vitamin C 0.15 mg.%) no fasting gastric acid; sella normal. Gained 11 lb. in 4 wk. on dietary regime, and 17-KS rose to 4.0 mg./24 hr.	1	—	2.4
4 (6399)	Anorexia nervosa	Female, 24 yr.; emaciated; amenorrhea 1 yr. preceding weight loss (114 to 84 lb.); FSH negative; marked improvement and gain of 9 lb. after psychiatric and dietary treatment.	6	3.8–9.8	7.2
5 (222698)	Anorexia nervosa	Female, 31 yr.; single; loss of 22 lb. during 4 yr.; amenorrhea and loss of hair for 1 yr.; B.P. 85/60; B.M.R. −35; FSH negative; x-ray studies non-contributory. No improvement on thyroid therapy.	1	—	3.6
6 (188740)	Malnutrition; ?anorexia nervosa	Female, 23 yr.; nausea, anorexia, wt. loss, and fatigue since a period of unhappiness and mental strain 7 yr. previously; menses regular; spinal fusion for scoliosis 2 yr. previously; no organic disease found.	4	4.2–9.6	6.6
7 (43659)	Malnutrition ulcerative colitis; amenorrhea	Female, 26 yr.; followed starvation diet because of obesity; very rapid weight loss to under 100 lb. with development of amenorrhea and ulcerative colitis; marked hypochloremia and alkalosis.	3	0.7–1.5	1.0
8 (198395)	Ulcerative colitis	Female, 28 yr.; bloody diarrhea for 6 mo.; x-ray showed typical ulcerative colitis.	2	1.0, 2.0	1.5
9 (154480)	Malnutrition; gastro-colic fistula	Male, 31 yr.; developed gastro-colic fistula and diarrhea followed gastro-enterostomy for duodenal ulcer; 36 lb. loss in weight in the year before admission; condition poor and not improved by medical treatment.	2	1.0, 3.3	2.2
10 (214067)	Terminal ileitis; steatorrhea; deficiency of all fat-soluble vitamins	Female, 35 yr.; operations for terminal ileitis; had various anastomoses; amenorrhea; wt. loss 41 lb.; FSH negative; hypovitaminosis D with tetany, hypovitaminosis K with bleeding diathesis, hypovitaminosis A with xeroderma. Improved markedly with treatment (19) and 17-KS assays rose to 7.2 mg./24 hr.	4	<0.5–<0.5	<0.5
11 (160875)	Sprue	Female, 19 yr.; diarrhea and weight loss 9 mo.; amenorrhea and loss of hair 4 mo. FSH negative; no free gastric acid; fasting blood sugar 46 mg.%; total blood cholesterol 52 mg.%; wt. 83 lb. Responded to parental liver extract and 17-KS rose to 6.6 and 4.6 mg./24 hr.	2	1.8, 1.8	1.8

[1] The expression, "FSH negative," means that the follicle stimulating hormone in the urine was less than 10 M.U. per 100 cc. first morning specimen of urine. Such a finding in a patient with amenorrhea is strong evidence that the amenorrhea is on a pituitary basis rather than due to primary ovarian failure (18).

[2] I.T.T. = insulin tolerance test. For significance see discussion under 'Panhypopituitarism.'

TABLE 7. FIVE CASES OF DEBILITY DUE TO MISCELLANEOUS CAUSES

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
12 (202764)	Rheumatoid Arthritis	Female, 16 yr.; painless swelling and stiffening of hands for 1 yr.; wt. 99 lb., appearance younger than stated age; menarche 15 yr. with regular menses.	2	3.0, 3.6	3.3
13 (256514)	Ulcerative colitis; ileostomy; rheumatoid arthritis	Male, 26 yr.; developed ulcerative colitis 18 mo. ago; rheumatoid arthritis superimposed 8 mo. ago; ileostomy 6 mo. ago; some loss of weight and considerable muscular weakness. Sedimentation rate slightly increased; afebrile.	2	2.7, 3.1	2.9
14 (180125)	Anemia; hypogonadism	Female, 14 yr.; required repeated transfusions for aplastic anemia for which no cause had ever been found; undersized, frail, thin; had not developed sexually.	2	1.4, 2.7	2.1
15 (255573)	Cooley's anemia	Male, 21 yr.; yellow-colored skin and coffee-colored urine since 5 yr. old; mongoloid appearance; slight jaundice; huge spleen and enlarged liver; R.B.C. 1.4 M; Hgb. 25%; FSH negative.	4	4.5–6.3	5.0
16 (237419)	Adenocarcinoma of rectum	Female, 46 yr.; developed adenocarcinoma of rectum metastasizing to bone; moderately thin and weak; Hgb. 80%; high serum Ca, P, and phosphatase.	1	—	2.1

the assay, but further studies are necessary to decide whether the observed changes were due to the operations or to drugs. Such studies as are completed strongly suggest that infections, surgical operations, anemia, in fact almost every sort of non-specific trauma lower the 17-KS excretion. For example, one of the male members of our staff, whose normal range was 10.3 to 11.3 mg./24 hr., during an upper respiratory infection excreted only 5.2 and 5.4 mg./24 hr. This apparent effect of non-specific trauma on 17-KS excretion is of interest and a little surprising in view of the work of Selye (20) who in his studies of the effect on the organism of non-specific trauma ('alarm reaction') found adrenal hyperplasia. Furthermore, Weil and Browne (21) found by biological assay an increased urinary excretion of 'cortin' in postoperative patients and patients with infections. Thus it would appear that the 17-KS assay probably is not a measure of cortical hormone production under these circumstances. The facts would be explained if one hypothesized that those urinary 17-ketosteroids which are derived from the adrenal cortex only appear in the urine in increased amounts when their production or that of their precursors is increased out of proportion to the need for them (see also section on acromegaly).

3. *Liver disease* (table 8). The very low values found in cases of liver disease are noted separately because they may have a more specific significance. Steroids are for the most part not excreted in the free form; conjugation probably occurs in the liver; in liver disease, therefore, 17-KS assays may be low because of failure of conjugation. Liver disease, furthermore, may effect steroid metabolism by its effect on fat absorption (cf. cases of steatorrhea, table 6).

4. *Hypoadrenocorticism* (*Addison's disease*) (table 9). If one assumes that all urinary 17-ketosteroids are derived from the male gonads and the adrenal cortex, and if in round numbers the average normal excretion for females is 9 mg. and for males 14 mg. per 24 hours, one would surmise that 9 mg. came from the adrenal cortex and 5 mg. from the male gonads. Furthermore, one would expect in Addison's disease that a female patient would have a negative assay result and that a male patient might excrete 5 mg. or less of 17-KS per 24 hours. It might be less than 5 mg. because the accompanying general debility might also lower the 17-KS production by the testis. In table 9 it will be seen that all 5 female patients with Addison's disease actually did have negative 17-KS assay results, while in the male patients the assays were all below 5 mg. but not negative. Unfortunately for establishing the point that the ovary does not produce any 17-KS, none of our female patients were still having regular periods, though this sometimes happens in well advanced Addison's disease. Less extensive lowering of the 17-KS assay in Addison's disease was found by Callow, Callow and Emmens (22), but all their cases were receiving hormone therapy and no clinical data are available. Furthermore, the correction method for impurities used in this laboratory (vide supra) may lead to virtually zero assays (less than 0.5 mg. per 24 hours) where other laboratories would have obtained low values.

5. *Hyperadrenocorticism* (table 10). It seems probable that at least three syndromes are to be attributed to an hyperadrenocorticism of some kind. These are: Cushing's syndrome, adreno-genital syndrome, and a feminizing syndrome in adult males.

TABLE 8. NINE CASES OF LIVER DISEASE

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
17 (22663)	Jaundice	Male, 54 yr.; jaundice, anorexia and wt. loss 6 wk.; esophageal varices; stools showed occult blood; Van den Bergh 30.4 mg.% direct; plasma prothrombin very low; urine contained sugar, albumin and 4+ bile. Vomited everything and failed rapidly.	2	0.7, 1.5	1.1
18 (229930)	Catarrhal jaundice?; common duct stone?	Male, 53 yr.; jaundice and anorexia 6 wk.; spleen palpable; Van den Bergh 26 mg.%; blood vitamin A low; stools clay colored. Later improved with fall in Van den Bergh.	5	3.5–8.5	5.5
19 (227404)	Jaundice; ?cirrhosis	Female, 34 yr.; intermittent jaundice 8 yr. Liver and spleen enlarged; Van den Bergh 2.7 mg.%. G.I. series showed esophageal varices.	3	0.5–3.5	2.0
20 (68467)	Biliary cirrhosis; jaundice	Female, 56 yr.; long history of gall bladder disease; cholecystectomy in the past; now complaining of jaundice, diarrhea, anorexia and weight loss; x-ray showed marked osteoporosis of spine presumably related to menopause; cachectic; liver large and firm.	2	<0.5, <0.5	<0.5
21 (221008)	Enlarged liver; no jaundice	Female, 18 yr.; unexplained fever, general glandular enlargement and hepatosplenomegally, anemia and eosinophilia; blood prothrombin level and liver function (bromsulphthalein test) low.	4	1.6–2.0	1.8
22 (224520)	Cirrhosis; cholemia	Male, 54 yr.; chronic alcoholic; jaundice 3 mo.; loss of 20 lb. in past yr.; anorexia and vomiting past few wk.; liver large and tender; emaciated; failed steadily.	2	1.1, 1.2	1.2
23 (237845)	Cirrhosis	Male, 57 yr.; ascites due to alcoholic cirrhosis; liver function low (bromsulphthalein test 35% dye retention).	2	2.0, 2.1	2.1
24 (11527)	Obstructive jaundice due to stones	Female, 53 yr.; jaundice 5 wk.; liver palpable; hypertension, cardiac enlargement; Van den Bergh 8.9 mg.%; chronically diseased, contracted gall bladder and 1.5 cm. stone in common duct found at operation. Convalescence uneventful.	3 (*Pre-op.*) 9 (*Post-op.*)	2.4–3.3 2.4 (after 5 days) 1.8 (after 8 days) 3.3 (after 9 days) 2.2 (after 10 days) 4.5 (after 11 days) 1.8 (after 12 days) 2.2 (after 19 days) 2.1 (after 20 days) 3.3 (after 21 days)	2.9
25 (241747)	Biliary cirrhosis	Female, 38 yr.; jaundice 2 yr., aggravated by fried foods; light stools; R.U.Q. pain; oozing of gums following extraction of teeth; no gall stones found at operation but biopsy showed biliary cirrhosis. After operation developed more pain, oozing and anorexia with icterus unchanged. Liver enlarged; vitamin C normal; plasma prothrombin very low; Van den Bergh 9.7 mg.%, biphasic. After 10 days of vitamin K therapy, prothrombin normal. Van den Bergh 24.7%, biphasic; 17-KS 2.8 mg.	2 (*Untreated*)	1.8, 1.8	1.8

By Cushing's syndrome is meant a definite disease picture, the most distinguishing features of which are muscular weakness, atrophy of the skin, osteoporosis of the bones, hirsutism without other evidence of virilism, insulin resistant diabetes, and amenorrhea or impotence. Since all cases of Cushing's syndrome have this extraordinary array of clinical features, it would seem likely that they must all be due to the same etiological factor. Some cases are definitely due to an adrenal cancer and hence presumably to an hyperadrenocorticism; it is therefore most likely that the cases without adrenal cancer likewise have an hyperadrenocorticism even though the adrenals show no definite hyperplasia. Assays were made on 5 cases of Cushing's syndrome. Two cases (cases 34 and 35) had adrenal cancer and ran very high assays. Three cases

TABLE 9. EIGHT CASES OF ADDISON'S DISEASE, FIVE FEMALES AND THREE MALES

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
26 (210582)	Addison's disease	Female, 23 yr.; irregular menses for 3 yr.; weakness, nausea, diarrhea, 25 lb. loss, amenorrhea, and pigmentation of skin for 1 yr.; thin and deeply bronzed; B.P. 80/60; I.T.T. showed marked hypoglycemia unresponsiveness (for significance see discussion on 'Panhypopituitarism').	6	<0.5–<0.5	<0.5
27 (228111)	Addison's disease	Female, 64 yr.; tuberculous hip in childhood; fatigue and weakness 6 yr.; pigmentation of skin 2 yr.; anorexia and nausea 6 mo.; B.P. 90/68; B.M.R. −24; serum Na 130 m.eq./l.; FSH negative. Autopsy showed complete caseation of both adrenals.	3	<0.5–<0.5	<0.5
28 (209947)	Addison's disease	Female, 45 yr.; emergency admission because of vomiting and diarrhea; weakness 2 yr.; characteristic pigmentation; B.P. 90/65; serum Na 141 m.eq./l.	3	<0.5–<0.5	<0.5
29 (188509)	Addison's disease	Female, 33 yr.; pulmonary tuberculosis in the past; classical signs and symptoms of Addison's disease. Serum Na 131 m.eq./l.; serum Cl 94 m.eq./l. Improved by adrenal cortical extract.	6	<0.5–<0.5	<0.5
30 (53949)	Addison's disease	Negress, 50 yr.; symptoms began at menopause, 5 yr. ago; increased pigmentation; weakness, weight loss; cervical adenitis; B.P. 90/70; serum Na 123.6 m.eq./l.; serum K 5.4 m.eq./l.; autopsy 1 yr. later confirmatory.	2	<0.5, <0.5	<0.5
31 (153528)	Addison's disease	Male, 58 yr.; loss of weight, weakness, vomiting, diarrhea, and bronzing of skin 3 yr.; received 5 cc. eschatin twice weekly past year; B.P. 120/75; serum Na 141 m.eq./l.	6	1.5–4.1	2.6
32 (258599)	Addison's disease	Male, 33 yr.; pleurisy (?) 3 yr. ago; renal colic and passage of stones 2 yr. ago; insidious onset of weakness and dizziness on exertion 18 mo. ago; progressive pigmentation 1 yr.; anorexia, loss of 40 lb., dyspnea on exertion and sensitivity to cold, 8 mo.; B.P. 102/72; lung x-ray: slight thickening of apical pleura; x-ray of adrenals: no calcification; tuberculin test positive; serum Na 132 m.eq./l.	6	1.2–2.8	2.1
33 (Private Patient)	Addison's disease	Male, 43 yr.; fatigue, weakness, wt. loss; pigmentation, and falling hair 3 yr.; tuberculosis in childhood; typical pigmentation; B.P. 95/70; serum Na 129 m.eq./l. Took salt and adrenal cortical extract regularly.	3	1.6–6.4	3.5

did not have adrenal cancer and these showed slightly high or high normal assays. If one considers the debility which all these patients have, even a normal value becomes significantly high. These findings in the non-cancer patients support the above hypothesis that all cases of Cushing's disease exhibit an hyperadrenocorticism.

The adreno-genital syndrome differs from Cushing's syndrome in having increased musculature instead of weakness, hirsutism with virilism instead of hirsutism without virilism, and less tendency to diabetes. The condition may be produced by tumors of the adrenal, benign or malignant, or by hyperplasia. Its clinical features vary depending on time of onset; it produces virilism in adult women and girls, precocity in boys, and pseudo-hermaphroditism in female fetuses. This latter syndrome is the one described by Young (23), and Howard and Whitehill (24) (see cases 39 and 42). The 17-KS assays were high in all the four cases with adreno-genital syndrome, the highest value being 220 mg./24 hr. in *case 40* with a tumor of one adrenal. Cases of pubertas precox in the female when due to hypothalamic lesions (see cases *131* and *132*, table 18) on the contrary do not have increased 17-KS excretion. Our experience with the adreno-genital syndrome and with those cases of Cushing's syndrome with adrenal tumors substantiates that of Callow and others (6, 25–28).

No cases with the feminizing syndrome have been studied, but high 17-ketosteroids have been found by other investigators (Burrows, Cook, Roe, and Warren (9) in the case reported by Simpson and Joll (29)).

6. '*Panhypopituitarism*' (table 11). By panhypopituitarism is meant absence or under-function of all the hormones of the anterior pituitary. The condition includes pituitary dwarfism, Simmonds' cachexia, and also some patients who are not cachectic. The more important clinical features of the condition are:

TABLE 10. NINE CASES OF PROBABLE HYPERADRENOCORTICISM: 5 CASES OF CUSHING'S SYNDROME (2 WITH ADRENAL CANCER, 3 WITHOUT), AND 4 CASES OF ADRENO-GENITAL SYNDROME

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
34 (110122)	Cushing's disease; cancer of adrenal	Female, 56 yr.; weakness, hirsutism, baldness, dyspnea, palpitation, pain in back, acne and florid face 2 yr.; B.P. 170/100; B.M.R.+32; G.T.T.[1] showed hyperglycemia unresponsiveness; FSH slightly positive; x-ray showed decalcification of spine. At autopsy an adrenal carcinoma weighing about 1 kg. was found.	1	—	74.0
35 (Old MGH)	Cushing's disease; cancer of adrenal	Female, 36 yr.; hypertrichosis of face, body and arms 14 mo.; furunculosis, kidney stones, obesity, decrease in stature, and edema of hands, wrists and ankles 9 mo., girdling chest pain 8 mo.; headaches; husky and deep voice 5 mo.; amenorrhea 6 mo.; easy bruisability; B.P. (systolic 170 to 135); R.B.C. 6 M.; heart enlarged to left; FSH negative. G.T.T. showed hyperglycemia unresponsiveness; decalcification of spine with deformed vertebrae. Autopsy showed malignant tumor of lt. adrenal with metastases to lymph nodes (30); no basophil tumor of pituitary.	2	20.3, 19.5 (made on urine stored at room temperature for 5 years).	19.9
36 (3397)	Cushing's disease	Female, 49 yr.; obesity, hirsutism, amenorrhea and ruddy complexion 8 yr.; diabetes, exertional dyspnea, tendency to bruise and back pain 5 yr.; both adrenals explored 4 yr. before (no tumor found); x-ray treatment to pituitary given for 2 yr. without benefit; osteoporosis and fractures of spine kept patient in bed 2 yr. B.P. 146/86.	10	9.2–36.0	19.7
37 (74372)	Cushing's disease	Female, 26 yr.; obesity, hirsutism, amenorrhea, striae, tendency to ecchymosis, and headache 7 yr.; osteoporosis of spine; B.P. 158/102; coronary heart disease; G.T.T. showed hyperglycemia unresponsiveness. Adrenal exploration negative; x-ray to sella produced some improvement.	6	7.5–13.5	10.4
38 (234190)	Cushing's disease	Female, 43 yr.; headache and fatigue 16 yr.; obesity 14 yr.; plethora of face 13 yr.; amenorrhea; increasing weakness 4 yr.; P.E. showed typical plethoric moon face, abdominal striae; atrophied skin and easy bruisability. G.T.T. showed hyperglycemia unresponsiveness; I.T.T. showed insulin resistance; osteoporosis. Autopsy showed adrenal hyperplasia and basophil adenoma of pituitary.	5	7.6–13.8	11.5
39 (169536)	Adreno-genital syndrome (pseudohermaphroditism); adrenal hyperplasia	Female, 5½ yr.; pseudohermaphroditism, enlarged clitoris at birth increasing since. Child unusually large and muscular for age; B.P. 122/86; tendency to acne; small amount pubic hair; bone age 9–11 yr.	32	8.2–21.5	12.6
40 (219534 C.H.[2])	Adreno-genital syndrome; adrenal tumor	Female, 3½ yr.; enlarged clitoris since birth; pubic hair, acne, deep voice; body hair abundant; clitoris measured 3½ cm.; bone age 9–10 yr. Ht. 42″; B.P. 116/80. An encapsulated tumor of fetal adrenal cortical tissue weighing 110 gm. was removed from right adrenal.	2	132.0, 220.0	176.0
41 (142513 C.H.[2])	Adreno-genital syndrome; unilateral adrenal hyperplasia	Male, 8 yr.; precocious sexual development appeared at 4 yr.; ht. 58″; wt. 80 lb.; musculature that of an adolescent; marked acne; penis and pubic hair well developed, prostate enlarged; bone age 12 yr.; B.P. 120/95; G.T.T. showed hyperglycemia unresponsiveness; cholesterol 88 mg.; B.M.R. normal. At operation a normal right adrenal was seen and a markedly but uniformly enlarged left adrenal was removed, with clinical improvement.	2	26.4–32.0	29.2
42 (Private)	Adrenal hyperplasia	Female, 23 yr.; amenorrhea and baldness; growth excessive until 13 yr.; obesity since 11 yr.; low voice and abdominal striae several yr.; never menstruated; uterus minute, no ovaries felt, clitoris greatly enlarged; no breast development, hirsutism, hair of scalp scant. Peri-renal air injection showed large adrenals on both sides.	4	64.4–82.6	72.4

[1] G.T.T.—glucose tolerance test.

[2] Previously reported (28). The authors are indebted to Drs. Allan Butler and Nathan Talbot of the Children's Hospital, Boston, for the opportunity of assaying the urine of these patients.

TABLE 11. FIFTEEN CASES OF PANHYPOPITUITARISM

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
43 (177833)	Panhypopituitarism following pregnancy	Female, 30 yr.; weakness, fatigue, depression, sensitivity to cold, dyspnea, amenorrhea, and loss of libido since 2nd childbirth, 7 yr. before; inversion of uterus and hemorrhage at time of delivery. Appearance typical of myxedema; B.M.R. −40, −50; cholesterol 112 mg.%; I.T.T. showed hypoglycemia unresponsiveness; FSH negative; Hgb. 52 to 60%; R.B.C. 4.2 M.; Ekg. typical of myxedema. Treatment with thyroid precipitated coma similar to Addisonian crisis with hypoglycemia (blood sugar level 18 to 42 mg.%) and low serum Na (total base 134 m.eq./l.).	4	<0.5–<0.5	<0.5
44 (160451)	Panhypopituitarism following pregnancy	Female, 35 yr.; amenorrhea since profuse hemorrhage at 2nd childbirth 9 yr. before; anemia; B.M.R. −23; cholesterol 367 mg.%; FSH negative; I.T.T. showed hypoglycemia unresponsiveness.	3	<0.5–<0.5	<0.5
45 (221187)	Panhypopituitarism following pregnancy	Female; 30 yr.; amenorrhea, weakness, nervousness, anemia and loss of hair since birth of twins 5 yr. before; dry atrophic skin, scant body hair; uterus small, external genitalia atrophied; I.T.T. showed hypoglycemia unresponsiveness; FSH negative; B.M.R. −4, −9; Ht. 54.7″, span 58.4″; wt. 76 lb.	2	1.3, 1.5	1.4
46 (171952)	Panhypopituitarism	Male, 45 yr.; pallor, weakness, hypersensitivity to cold; loss of hair and impotence for 20 yr. Because of thick, pale, cold, dry, hairless skin had been treated for myxedema without benefit; B.M.R. −20; I.T.T. showed hypoglycemia unresponsiveness.	16	<0.5–<0.5	<0.5
47 (218519)	Panhypopituitarism (?); small stature; obesity; (alternative diagnosis: eunuchoidism with negative FSH; see section on "Male Hypogonadism")	Male, 38 yr.; ht. 59.3″, span 62.9″, wt. 152 lb.; short, plump, childish looking; always small, gaining weight since age of 20; never shaved; always constipated; always sensitive to cold; mumps with orchitis at 12 yr.; small but descended testes, minute prostate; x-ray of skull negative, of left hip showed Legg-Perthe's disease; B.M.R. +5; bone age 14 yr. I.T.T. equivocal.	3	<0.5–<0.5	<0.5
48 (187779)	Panhypopituitarism; dwarfism	Female, 45 yr.; backache, a fragile-looking, prematurely-aged little woman with childlike voice and face; no breast development, no body hair, genitalia infantile, skin fine and atrophic; x-ray showed diffuse osteoporosis, ununited epiphyses of right knee and phalanges, slipped radial epiphysis and Osgood-Schlatter's disease; B.M.R. −6; FSH negative; I.T.T. showed hypoglycemia unresponsiveness.	2	<0.5, <0.5	<0.5
49 (189660)	Panhypopituitarism; dwarfism	Female; 20 yr.; ht. 46.8″, wt. 50 lb.; growth not normal since 3 yr. of age; breech delivery with severe cyanosis and 2 convulsions during 1st yr. of life; 2 head injuries with unconsciousness at ages 10 and 12 yr.; weak, disliked cold; no puberty; appearance that of 10 yr. old child; x-ray showed retarded bone age, normal sella turcica; B.M.R. −33; no response to thyroid treatment; I.T.T. showed hypoglycemia unresponsiveness.	4	<0.5–<0.5	<0.5
50 (234043)	Panhypopituitarism; dwarfism	Male, 14 yr.; small, undeveloped, immature looking; bone age retarded; B.M.R. −24; −27; no mental impairment; I.T.T. normal.	2	<0.5, <0.5	<0.5
51 (199523)	Panhypopituitarism; dwarfism	Male, 17 yr.; ht. 54.8″; span 55.7″; wt. 71¾ lb.; under observation since age of 13; first noticed lack of growth at age of 5; no secondary sex development; P.E. showed typical pituitary dwarf; genitalia normal for prepuberty; patient received 1 gr. thyroid daily and grew at the rate of about 1.2″ a yr.; marked retardation in bone age; I.T.T. showed hypoglycemia unresponsiveness; FSH negative.	3	<0.5–<0.5	<0.5

TABLE 11—*Continued*

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
52 (64011)	Panhypopituitarism; dwarfism	Male, 14 yr.; ht. 49.9″; span 48.2″; wt. 55 lb.; under observation 3 yr.; considered normal until 5 yr., very little growth since; P.E. showed typical pituitary dwarf; B.P. 85/60; caries of teeth; had one episode of hypoglycemia after initiation of thyroid therapy; B.M.R. −10; bone age approximately 8 yr.; FSH negative.	4	<0.5–<0.5	<0.5
53 (83970)	Panhypopituitarism; cranio-pharyngioma; dwarfism	Male, 19 yr.; ht. 56.5″; wt. 68.2 lb.; cranio-pharyngeoma partially removed at 11 yr. because of visual disturbances and polydipsia; convulsions brought patient under observation 8 yr. later, and he then exhibited pituitary cachexia with stunted growth, sexual infantilism and progeria.	4	<0.5–<0.5	<0.5
54 (196847)	Panhypopituitarism; cranio-pharyngioma	Female, 24 yr.; amenorrhea 3 yr.; headache, drowsiness, failing vision 8 mo.; at operation an extensive cranio-pharyngeoma was partially removed; FSH negative before operation. After operation 17-KS assays rose to 6.0 and 6.5 mg./24 hr.; one of two FSH tests positive, I.T.T. normal.	2	<0.5, <0.5	<0.5
55 (156946)	Panhypopituitarism; pituitary tumor	Female, 28 yr.; amenorrhea 6 yr.; headache and fatigue 5 yr.; cold and drowsy; lost 50 lb.; x-ray showed enlargement of sella; each of 2 courses of radiation treatment produced improvement; I.T.T. showed hypoglycemia unresponsiveness; B.M.R. −21; FSH negative; urinary estrin negative.	4	<0.5–<0.5	<0.5
56 (167602)	Panhypopituitarism; brain tumor	Male, 41 yr.; increasing thirst for 2 yr.; obesity, weakness, and impotence 1½ yr.; cranial nerve palsies, diplopia and vomiting last few wk.; neurological signs of 3rd ventricle tumor; I.T.T. showed hypoglycemia unresponsiveness; death in coma. Autopsy showed intrasellar tumor with destruction of most but not all of pituitary.	2	<0.5, <0.5	<0.5
57 (122676)	Panhypopituitarism; suprasellar cyst	Male, 55 yr.; entered 6 yr. before for visual disturbances and was found to have a cyst on or near sella turcica which was only partially removed; returned because of anorexia, nausea, loss of 75 lb., weakness, slow speech, and sensitivity to cold; B.M.R. −2; still obese, pasty, soft hair and skin; body hair decreased; testes small; serum Na low (129.6 m.eq./l.); I.T.T. did not show hypoglycemia unresponsiveness. Died following pituitary exploration; autopsy showed small rim of normal pituitary still remaining.	3	<0.5–2.8	1.8

weakness, usually loss of weight, often loss of axillary and pubic hair, amenorrhea with 'negative FSH tests'[4] in females, impotence and loss of libido in males, symptoms suggestive of hypothyroidism with low B.M.R.'s, dwarfism with retarded bone age when the condition occurs in children, and tendency to hypoglycemia with an inability to compensate for an insulin induced hypoglycemia. The abnormality in the sugar metabolism is best brought out by performing an insulin tolerance test (I.T.T.). Patients with adrenal-cortical insufficiency (panhypopituitarism or Addison's disease) are unable under fasting conditions to raise the blood sugar level once it has been depressed by insulin because of impaired gluconeogenesis (31).

Since the pituitary stimulates both the adrenal cortex and the male gonads, one would expect all patients with panhypopituitarism to show very low 17-KS assays; this is true but, what is even more significant, of our 15 cases only two (cases 45 and 57) showed any detectable 17-KS in the urine at all. *Case 45* was a very mild example of the condition, and *case 57* at autopsy had a small remnant of normal pituitary still remaining and also did not show the unresponsiveness to an insulin induced hypoglycemia. The etiology in three of our 15 cases (cases 43, 44, 45) was probably that described by Sheehan (32) of pituitary infarction following a severe hemorrhage at childbirth. *Case 54* is of interest in that after the partial removal of a cranio-pharyngioma, the cause of the condition, the 17-KS assay rose from <0.5 to 6.5 mg. per 24 hr., and the FSH test became positive.

7. *Acromegaly* (table 12). Since the adrenal cortex

[4] See note at bottom of table 6.

TABLE 12. SIX CASES OF ACROMEGALY, FIVE FEMALES AND ONE MALE

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
58 (*195410*)	Acromegaly; amenorrhea	Female, 28 yr.; headache and amenorrhea 1 yr.; enlargement of hands, feet, and nose; B.M.R. +7, +38; x-ray showed enlarged sella; G.T.T. normal; FSH negative.	4	3.6–6.0	4.5
59 (*135659*)	Acromegaly; amenorrhea	Female, 43 yr.; classical acromegaly; amenorrhea since last pregnancy 22 yr. before; enlargement of face and extremities 15 yr.; wt. gain, headaches, and dizzy spells 10 yr. FSH negative; G.T.T. showed hyperglycemia unresponsiveness. Radiation of pituitary relieved headache.	5	2.0–5.3	2.9
60 (*110968*)	Acromegaly; amenorrhea	Female, 36 yr.; amenorrhea 4 yr.; headache, acne and mild hirsutism 3 yr.; face and hands suggest acromegaly; x-ray showed enlarged sella; FSH negative. Radiation of pituitary relieved headache.	2	10.5–10.6	10.6
61 (*165072*)	Acromegaly	Female, 35 yr.; face, hands and feet enlarging 10 yr.; normal pregnancy 2 yr. ago; x-ray of extremities and sinuses typical of acromegaly; G.T.T. showed hyperglycemia unresponsiveness; FSH negative. Radiation of pituitary relieved headache.	2	10.0–10.4	10.2
62 (*30560*)	Acromegaly; amenorrhea	Female, 41 yr.; amenorrhea, hirsutism, large features and extremities, headache, poor vision, enlargement of sella by x-ray. G.T.T. showed hyperglycemia unresponsiveness; FSH negative.	5	2.1–5.6	3.6
63 (*63267*)	Acromegaly	Male, 31 yr. enlargement of hands, feet, and jaw 10 yr.; 2 children—5 and 3½ yr. libido normal; x-ray showed normal sella, large sinuses; G.T.T. normal.	2	8.0–8.7	8.3

is markedly hypertrophied in acromegaly, one might expect an increase in the 17-KS assay in this condition. This is not the case; the assays are either normal or slightly low. The hypothesis suggests itself that the hypertrophy is compensatory and that any increased need for cortical hormone decreases the 17-KS excretion (see discussion under *Debility from other causes*). It is of interest that Dr. P. G. Weil found a marked increase in the 'cortin' excretion in the urine of *case 58* with the biological method (21). Six cases were studied, 1 male and 5 females; the results were low in 3 and normal in 3.

8. Male hypogonadism (table 13). In this section are considered those cases of male hypogonadism not due to panhypopituitarism. There were three cases of surgical castration (cases *64*, *65*, *66*), but of these only *case 64* was uncomplicated (*case 65* had infection; *case 66* had muscular dystrophy). The average of nine 17-KS assays in *case 64* was 7.0 mg. per 24 hours which is about the degree of lowering one might expect. For, if the inference is correct that the 17-ketosteroids are derived from the male gonads (circa 5 mg.) and the adrenal cortices (circa 9 mg.), the values in a male castrate should fall into the normal female range. The findings in our case are in agreement with 2 of the following 3 cases studied by Callow et al. (33, 34) [*Case A*, age 20: 9.4, 10.9 mg./24 hr.; *case B*, age 38, gonadectomy due to gun shot wound: 8.4, 7.2 mg./24 hr.; *case C*, age 45, gonadectomy due to tuberculosis: 3.1 mg./24 hr.]. The lower values in our cases *65* and *66* may have been due to the complications. In *case 65* as a matter of fact the 17-KS assay was already on the low side (7.3 and 7.8 mg./24 hr.) before the second testis was removed when the assay fell immediately to 2.8 mg. to return to 5.4 mg. per 24 hr. in 18 days. In the two of these three patients on whom FSH tests were made, the results were, of course positive, indicating the underfunction to be primarily gonadal (18). Since cases *67*, *68* and *69* likewise had positive FSH test results, they were probably examples of castration due to disease. Indeed, *case 67* gave a history of orchitis during the first few days of life; his 17-KS assays averaged 8.5 mg./24 hr. *Case 68* had an assay in the same range (8.4 mg.), but *case 69*'s assay was unexplainably low (2.7 mg./24 hr.).

In contrast to cases *67*, *68* and *69* are patients *70* through *78*, who will be discussed in more detail by Fraser, Miller and Albright (35). They represent a most interesting group, and all had essentially the same characteristics: lack of secondary sex development; delayed epiphyseal fusion with their spans greater than their heights; bilateral absence of testes in the scrotum or, more commonly, very small testes; prostates which could not be felt by rectum; negative FSH test results; and, with certain exceptions which will be discussed below, definite rises in the 17-KS assay following chorionic gonadotropin therapy. The question arises as to what is the primary endocrine

TABLE 13. FIFTEEN CASES OF MALE HYPOGONADISM: 3 GONADECTOMIZED INDIVIDUALS, 3 CASES OF PRIMARILY GONADAL HYPOFUNCTION, AND 9 CASES OF IDIOPATHIC EUNUCHOIDISM

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
64 (100777)	Male castrate	47 yr.; bilateral orchidectomy for malignant adenoma of testes 8 yr. before; some change toward eunuchoid habitus and loss of sexual powers; FSH positive.	9	5.7–9.3	7.0
65 (199436)	Male castrate	66 yr.; unilateral orchidectomy for infection secondary to carcinoma of prostate; second testis removed for infection 5 wk. later; 17-KS before second operation 7.3 and 7.8 mg./24 hr.	6	2.8 (3 days after 2nd operation) 5.4 (18 days after 2nd operation)	4.1
66[1]	Male castrate	54 yr.; bilateral gonadectomy at 21 yr.; obese and eunuchoid in appearance; hypospadias; FSH positive; also marked muscular dystrophy and a long psychopathic history. No rise in 17-KS with chorionic gonadotropin therapy.	4	2.3–3.6	3.2
67 (Private patient)	Partial eunuchoidism with positive FSH. Orchitis as infant	18 yr.; ht. 69.8″; span 75.2″; wt. 152.5 lb.; history of orchitis at 3 days of age; normal sexual development, no beard, high voice, body hair scant to normal, penis fairly normal, no prostate felt; FSH positive twice. At operation remnant of right but no left testis found. No rise in 17-KS with chorionic gonadotropin therapy.	4	8.1–9.0	8.5
68 (110345)	Eunuchoidism with positive FSH	25 yr.; ht. 73.2″; span 78.7″; wt. 164.3 lb.; no sexual development; beardless, scant pubic hair, prostate not felt, penis infantile, scrotum empty; bone age delayed; B.M.R. −2; FSH positive. No rise of 17-KS excretion with chorionic gonadotropin therapy.	5	6.7–9.6	8.4
69 (127979)	Eunuchoidism with positive FSH	20 yr.; ht. 67.3″; span 72.0″; cryptorchidism; bone age and sexual development retarded; operation disclosed only a small fibrous remnant of right testicle. Still had soft skin, no beard, high voice, small penis, and scant pubic hair. FSH positive for 30 M.U./100 cc.	2	2.6, 2.2	2.4
70 (72110)	Eunuchoidism with negative FSH	29 yr.; ht. 73.2″; span 73.6″; wt. 165.5 lb.; lack of sexual development; boyish looking, smooth face, high voice, scant axillary and pubic hair, small penis, small testes in scrotum, no prostate palpable; skeleton immature; FSH negative. 17-KS response to chorionic gonadotropin therapy equivocal.	2	6.4, 6.4	6.4
71 (101990)	Eunuchoidism with negative FSH	35 yr.; ht. 68.7″; span 71.7″; wt. 140 lb.; no sexual development, beard and pubic hair absent; prostate not palpable; testes size of olive stones; B.M.R. −9, FSH negative; x-ray showed epiphyses still ununited. Slight rise in 17-KS with chorionic gonadotropin therapy.	2	2.6, 3.3	3.0
72 (Private patient)	Eunuchoidism with negative FSH	21 yr.; ht. 72.4″; span 72.9″; wt. 146 lb.; never developed sexually; high voice, smooth face, scant body hair, infantile external genitalia, no prostate felt; small testes in scrotum; retarded bone age. FSH negative. Rise in 17-KS excretion with chorionic gonadotropin therapy.	2	4.2, 5.4	4.8
73 (32537)	Eunuchoidism with negative FSH	28 yr.; ht. 67¼″; span 75¼″; wt. 123 lb.; never matured sexually; genitalia infantile, small testes in scrotum, voice high-pitched, face smooth, body hair scant; epiphyses ununited; B.M.R. −5; FSH negative. Marked clinical response to chorionic gonadotropin therapy.	2	4.0, 4.3	4.2
74 (8446)	Eunuchoidism with negative FSH	19 yr.; ht. 61.4″, span 63.4″; wt. 99 lb.; no sexual development; infantile genitalia; left testicle size of a bean, right not palpable; FSH negative.	3	1.5–2.3	2.8
75 (Private patient)	Eunuchoidism with negative FSH	30 yr.; ht. 70.4″, span 71.6″; wt. 138 lb.; under-developed sexually; no beard or peri-anal hair; pubic hair female in distribution, little hair on extremities; testes very small; fairly strong; "normal" libido; rare nocturnal emissions; FSH normal.	Results of 17-KS assays in this patient had to be discarded because of faulty collections.		

TABLE 13—*Continued*

Case No. and hospital No.	Diagnosis	Clinical Data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
76 (113725)	Eunuchoidism with negative FSH	34 yr.; ht. 66″; span 69.3″; wt. 154 lb.; lack of sexual development; flabby; body hair scant, no beard, no prostate felt; penis very small, testes size of olive stones; FSH negative. Rise in 17-KS assay with chorionic gonadotropin therapy.	4	3.2–4.6	3.9
77 (Private patient)	Eunuchoidism with negative FSH	24 yr.; ht. 67.5″; span 68.5″; wt. 141 lb.; lack of secondary sex development; small testes in scrotum, no prostate felt; decreased pubic hair; small larynx, high voice, no beard; delayed bone age; FSH negative. 17-KS assay increased with chorionic gonadotropin therapy.	2	3.0, 3.9	3.5
78 (257144)	Eunuchoidism with negative FSH	21 yr.; ht. 61″; span 65″; wt. 106 lb.; hair-lip at birth; delayed dentition; growing slowly but steadily to present; voice changed 3 yr. ago; erections at times but no ejaculations; feels strong, not easily fatigued; general appearance that of boy of 14 yr.; smooth face, soft skin, scant torso hair; no visible thyroid cartilage; penis very small; scrotum under-developed, testes absent, prostate not palpable, muscles small but strong; bone age about 15 yr.; B.M.R. normal; FSH negative. I.T.T. normal.	4	5.4–6.9	6.2

[1] The authors are indebted to Dr. Jerry C. Price, of the Boston City Hospital, and Dr. Roy D. Halloran, of the Metropolitan State Hospital, Waltham, Mass., for the specimens on this patient.

TABLE 14. TWENTY-THREE CASES OF FEMALE HYPOGONADISM: 13 CASES OF PRIMARILY OVARIAN HYPOFUNCTION, AND 10 CASES OF OVARIAN HYPOFUNCTION SECONDARY TO PITUITARY HYPOFUNCTION

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
		A. Surgical and Physiological Menopause			
79 (178793)	Menopause (surgical)	27 yr.; hot flashes; hot flashes since 2nd oöphorectomy 2 yr. before.	3	6.2–14.6	9.2
80 (180716)	Menopause (surgical)	33 yr.; hot flashes since bilateral oöphorectomy 1 yr. before; receiving estrin therapy regularly.	3	10.2–12.7	11.8
81 (183223)	Menopause (surgical)	30 yr.; bilateral oöphorectomy for dermoid cysts 1 yr. before.	1	—	11.9
82 (156453)	Menopause (surgical); osteoporosis	42 yr.; oöphorectomy 20 mo. before for endometriosis; post-menopausal osteoporosis; under estrin therapy.	5	2.8– 6.5	4.9
83 (17995)	Menopause (surgical)	45 yr.; severe menopausal symptoms following complete hysterectomy 1 yr. before.	2	6.8, 7.2	7.0
84 (20358)	Menopause (physiological); osteoporosis	63 yr.; menopause at 45 yr.; post-menopausal osteoporosis.	3	4.8– 7.2	6.0
85 (203540)	Menopause (physiological)	60 yr.; menopause at 53 yr.; post-menopausal osteoporosis; fractured vertebrae.	5	2.4– 4.3	3.8
		B. Syndrome: Primary Amenorrhea, Positive FSH Test, Dwarfed Stature			
86 (47830)	Ovarian amenorrhea; moderate dwarfism	21 yr.; ht. 56.5″; wt. 74 lb.; never menstruated; tired easily; no breast development; scant pubic and axillary hair; rudimentary uterus; FSH strongly positive; delayed epiphyseal union.	4	1.0	2.2
87 (133054)	Ovarian amenorrhea; moderate dwarfism	16 yr.; ht. 54″; span 57.4″; wt. 81 lb.; failure to grow and develop; no breast tissue, little axillary hair, genitalia infantile; menarche never occurred. Bone age retarded; x-ray showed normal sella; FSH positive.	2	2.1, 4.8	3.5

TABLE 14—*Continued*

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
88 (*181822*)	Ovarian amenorrhea	33 yr.; ht. 67.9″; span 75.5″; wt. 120 lb.; mumps at 5 yr.; axillary and pubic hair at 12 yr.; no menses or molimina; infantile genitalia; breasts infantile; epiphyses ununited; FSH positive.	2	4.7, 5.3	5.0
89 (*144936*)	Ovarian amenorrhea; dwarfism	29 yr.; ht. 55″; span 57.8″; wt. 140 lb.; never menstruated; no breast development, scant pubic hair, infantile genitalia; peritoneoscopy showed a "cobblestone liver," infantile uterus and no visible ovarian tissue; FSH positive; B.M.R. and x-ray of skull and epiphyses normal; G.T.T. and I.T.T. normal.	1	—	4.2
90 (*51984*)	Ovarian amenorrhea; dwarfism	20 yr.; ht. 54½″; wt. 88 lb.; never menstruated; hot flashes for 6 yr.; childish looking, no breast development or body hair, genitalia infantile except for rather large clitoris; bone age retarded; FSH positive.	6	4.1–6.6	4.7
91 (*330336, Old MGH*)	Ovarian amenorrhea; moderate dwarfism	21 yr.; ht. 56.2″; span 57″; wt. 104 lb.; never menstruated; genitalia small; little body hair, poorly developed breasts; B. Melitensis infection in past (?oöphoritis); FSH positive.	2	1.0, 2.9	2.0
		C. Pituitary Amenorrhea, Negative FSH Test			
92 (*230743*)	Amenorrhea	25 yr.; ht. 63.2″; span 67.3″; wt. 111 lb.; never menstruated; breast development absent; body hair scant, genitalia infantile; bone age retarded; FSH negative. Peritoneoscopy showed absent ovaries and uterus.	2	6.6, 5.4	6.0
93 (*171149*)	Amenorrhea	18 yr.; menarche 16 yr., regular menses until cessation 5 mo. ago; gain of 30 lb. past 3 yr.; diet poor in vitamin B; FSH negative; genitalia small; endometrium scant. No response to thyroid.	2	4.3, 5.1	4.7
94 (*228102*)	Amenorrhea	32 yr.; married but nulliparous; amenorrhea 6 yr.; menarche at 14 yr., menses about every 3 mo. till 26 yr.; then ceased; infantile uterus and atrophy of vaginal mucosa; FSH negative; skull x-ray, B.M.R. and G.T.T. normal.	2	3.6, 5.1	4.4
95 (*173620*)	Amenorrhea	18 yr.; never menstruated; normal secondary sex development at 14 yr.; pelvic exam. normal but no endometrium obtainable on biopsy; FSH negative; sella unusually small; I.T.T. normal.	1	—	4.8
96 (*236204*)	Amenorrhea	24 yr.; normal and regular menses from 11½ yr. until cessation 7 mo. ago; fatigability and weight gain 7 mo.; FSH negative.	2	7.8, 8.3	8.1
97 (*229892*)	Amenorrhea	18 yr.; never menstruated; tall, thin, poorly developed, scant pubic hair, no breast development, uterus not palpable, delayed bone age; FSH negative.	2	6.9, 7.4	7.2
98 (*159471*)	Amenorrhea	32 yr.; amenorrhea and sterility 6 yr.; physically normal except for juvenile uterus; little endometrium obtainable on biopsy; FSH negative; skull x-ray negative.	4	7.8–9.9	9.2
99 (Private patient)	Amenorrhea	27 yr.; menarche 13 yr., menses regular until 20 yr., then irregular for 1 yr.; absent past 6 yr.; physically normal except for atrophied vaginal mucosa, small uterus, and one palpable ovary; FSH negative.	3	12.3–17.1	14.3
100 (*226538*)	Amenorrhea	Italian, 29 yr.; sterility, amenorrhea 1 yr.; obese, hirsute; FSH negative; I.T.T., visual fields, and skull x-ray normal.	2	7.2, 9.3	8.3
101 (Private patient)	Amenorrhea; chromophobe adenoma	35 yr.; amenorrhea and obesity 1 yr.; genitalia atrophied; FSH negative; x-ray showed pituitary tumor. [N.B. Prolan A (1935) slightly positive.]	2	11.6, 11.2	11.4

TABLE 15. THREE CASES OF OVARIAN TUMORS

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
				Pre-operative	
102 (174195)	Arrhenoblastoma of ovary	30 yr.; hirsutism, obesity, amenorrhea, sterility 10 yr.; puberty normal, menses previously regular; large, masculine, deep voice, hairy face and body, beginning baldness of scalp, clitoris 4 cm.; palpable nodule on left ovary; G.T.T. normal. Following removal of arrhenoblastoma from left ovary, menses occurred within 1 mo., a secretory endometrium within 2 mo., pregnancy within 1 yr.	2	5.3, 8.5	6.9
				Post-operative	
			2	2.4 (1 wk. later), 3.9 (5 wk. later)	3.2
103 (176118)	Arrhenoblastoma of ovary (post-operative)	41 yr.; amenorrhea, 2 yr.; abdominal pain, ovarian arrhenoblastoma removed; menses returned 5 wk. later.		*Post-operative*	
			2	1.0, 3.6	2.3
				Pre-operative	
104 (231869)	Disgerminoma of ovary	19 yr.; blonde hirsutism of face and extremities, husky voice, slight acne, poorly developed breasts and enlarged clitoris. Disgerminoma removed from right ovary. FSH positive once before and once after operation.	5	7.1–9.0	7.8
				Post-operative	
			10	1.1–5.1	2.5

disorder. The fact that the FSH test results were uniformly negative makes it unlikely that the testes were primarily underfunctioning (cf. cases 64–69), and suggests primary pituitary disease. Such a conclusion is further suggested by the rise in 17-KS assay with gonadotropin therapy, a finding which is also present in panhypopituitarism in males, but which is not present in castrates (table 21). The 17-KS assays in 8 of these 9 patients were fairly uniform, the average values being 6.4, 3.0, 4.8, 4.2, 2.8, 3.9, 3.5, and 6.2 mg./24 hr. These are low figures when one considers that these individuals were all otherwise healthy young men. The hypothesis suggests itself that the hypogonadism in this group is not the only disorder, but that there is an associated underproduction of steroids by the adrenal cortex. If this is true, it is another indication that the primary disorder is in the pituitary.

There would, therefore, seem to be three sub-types of male eunuchoidism: *A*, that due to a panhypopituitarism in which the FSH test result is negative and the 17-KS assay result is likewise negative; *B*, that due to primarily gonadal underfunction in which the FSH test result is positive and the 17-KS assay result is that of a normal female, circa 9.0 mg./24 hr.; and *C*, that due to a pituitary underfunction which does not involve the entire anterior pituitary but which does involve the corticotropic hormone as well as the gonadotropic hormone, in which the FSH test result is negative and the 17-KS assay result is distinctly lower than that of a normal female. In this paper we refer to these three conditions as 'panhypopituitarism', 'eunuchoidism-with-positive-FSH,' and 'eunuchoidism-with-negative-FSH.' *Case 47*, table 11, is of interest in that his condition falls between the first and third of these diagnoses. He has been classified as a case of panhypopituitarism but against this diagnosis are the facts that he is obese and that he is not unresponsive to an insulin induced hypoglycemia. Against his diagnosis being eunuchoidism-with-negative-FSH is the fact that his 17-KS assay result is negative. Furthermore, he is fairly short. It is really impossible to decide whether he has a marked degree of 'eunuchoidism-with-negative-FSH' or a mild degree of 'panhypopituitarism."

9. *Female hypogonadism* (table 14). Since the 5 female patients with Addison's disease had negative 17-KS assay results, it seemed probable that the normal ovary is not a source of these substances. This point of view is supported by the work of Hirshmann (36), who isolated the three 17-ketosteroids which have been demonstrated in normal urine (table 1) from the urine of oöphorectomized patients in about the same proportions as in normals. Therefore, it is not surprising that young women who have undergone an artificial menopause have essentially normal values (see cases 79, 80, 81). Furthermore, since normal menopause, from an endocrine point of view, is essentially the same as artificial menopause except that the ovarian failure is due to physiological causes, one would expect to obtain normal findings in that condition. Such probably is the case if one allows for the effect of age (cases 84, 85).

Cases 86–91 are a very interesting group and probably constitute a syndrome, which, it is hoped, may be discussed more fully elsewhere. The characteristics of the syndrome are primary amenorrhea with no secondary sex development, positive FSH test results indicating primarily ovarian as opposed to pituitary failure, and moderate dwarfism (all except *case 88*). It is of interest that *case 88* who failed to show dwarfism had an abortive puberty at 12 years of age and may be a very early menopause precox. The 17-KS in all the patients in this group were low.

It is difficult to make an analysis of the results on

TABLE 16. NINE CASES OF THYROID DISEASE: 6 CASES HYPOTHYROIDISM, 3 CASES HYPERTHYROIDISM

Case No. and hospital No.	Diagnosis	Clinical notes	No. of assays	Range mg./24 hr.	Average mg./24 hr.
105 (202740)	Myxedema (post-operative)	Female, 47 yr.; tiredness, depression, and menorrhagia since thyroidectomy 3 yr. before; appearance typical of myxedema, skin edematous, cold and dry; B.M.R. −28; Wassermann reaction 4+.	3	<0.5–2.1	0.7
106 (234874)	Juvenile myxedema	Female, 14 yr.; under observation at 12 yr. for obesity, mental retardation and failure to grow for previous 5 yr.; at that time short, fat, dull; bone age and dentition retarded 5 yr. B.M.R. −28. Thyroid caused 8″ growth in 1 year; puberty just beginning at 14 yr. Not receiving thyroid at time of 17-KS assay.	1	—	1.8
107 (227433)	Myxedema	Female, 28 yr.; gain in weight, sleepiness, and decreased activity since first pregnancy 7 yr. before; second pregnancy 5 yr. before; menses scant 2 yr.; appearance characteristic, face puffy, hands and feet cold and puffy; cholesterol 312 mg.%; B.M.R. −40; FSH negative.	7	0.6–3.4	1.6
108 (213763)	Myxedema	Female, 63 yr.; increasing sluggishness, dry skin, and falling hair 10 yr.; appearance typically myxedematous; B.M.R. −31, cholesterol 342 mg.%.	3	<0.5–1.0	0.6
109 (Private patient)	Myxedema	Female, 29 yr.; increasing weight, dry, falling hair, and puffy hands and face 2 yr.; amenorrhea since birth of fifth child 5 mo. before; B.M.R. −40, cholesterol 312 mg.%; FSH negative.	5	1.0–2.2	1.6
110 (18190)	Myxedema	Female, 74 yr.; classical picture of myxedema; cholesterol 362 mg.%; FSH positive; B.M.R. −50 to −34.	3	1.3–1.5	1.4
111 (224076)	Hyperthyroidism	Female, 45 yr.; swelling in the neck, tremor, sweating for 14 months; goiter, tachycardia, lidlag; B.M.R. +59.	2	3.2, 4.8	4.0
112 (198201)	Hyperthyroidism	Female, 45 yr.; lost 60 lb. in 2 yr.; goiter 1½ yr.; exophthalmos, enlarged thyroid, cardiac enlargement and ankle edema; B.M.R. +89.	3	4.6–6.6	5.6
113 (218911)	Hyperthyroidism	Female, 28 yr.; goiter, nervousness, sweating, weight loss, and precordial pain; B.M.R. +33.	2	0.8, 1.8	1.3

patients with 'pituitary amenorrhea' because in any one case it is difficult to be sure of the diagnosis. By 'pituitary amenorrhea' is meant a condition where there is obvious hypo-ovarian function coupled with a negative FSH test result. Furthermore, we would like to consider here only those cases of 'pituitary amenorrhea' where the underfunction of the follicle stimulating hormone is both selective, in contrast to cases of panhypopituitarism, and primary, in contrast to cases where the hypofunction is secondary to malnutrition, general debility, or an excess of some pituitary inhibiting steroid (e.g. with an arrhenoblastoma or an adrenal cortical tumor). The syndrome under discussion may be the female counterpart of the group of patients diagnosed 'eunuchoidism-with-negtive-FSH' (vide supra). And, indeed, many of these cases tend to have low 17-KS assays which strengthens the analogy (cases 92, 93, 94, 95). There is no proof, however, in many of these cases (see *case* 93) that the amenorrhea and the low 17-KS assay results are not both due to malnutrition or general debility. Other patients (cases 96, 97, 98, 99, 100) have perfectly normal 17-KS assays. Here again, however, one cannot be too sure of the diagnosis in any one case. Thus, it is possible that *case* 100 with amenorrhea and hirsutism may have a small arrhenoblastoma; this is also a remote possibility in *case* 99 with the palpable ovary and amenorrhea. *Case* 101 is of interest in that it is clear from her x-ray that she has a tumor or a cyst in the pituitary fossa which apparently has interfered with the follicle stimulating hormone production without causing a panhypopituitarism. Her 17-KS assay was normal, 11.0 mg./24 hr.

10. *Ovarian tumors* (table 15). Three cases of tumor of the ovaries have been studied (cases 102, 103, 104). The first of these was a classical case of arrhenoblastoma with amenorrhea, sterility and virilism. A priori, one would have expected the 17-KS assay result to be high since an arrhenoblastoma presumably produces testosterone which is excreted as androsterone and aetiocholan—17 one—3α ol, both 17-ketosteroids. The values were well within the normal range but fell somewhat after the operation, and remained low even after her catamenia returned.

The authors are not aware of other observations on such cases in the literature. The possibility arises that this tumor may produce some steroid which is virilizing but which is not excreted as a 17-ketosteroid. *Case 103* also had an arrhenoblastoma, but her symptoms were confined to amenorrhea of two years, and did not include virilism. She is the type of case that might very easily be mistaken for 'pituitary amenorrhea' (vide supra). Unfortunately no assays were made on her preoperatively. Her post-operative values were fairly low. *Case 104*, a 19-year-old girl with primary amenorrhea and virilism, had at operation disgerminoma of one ovary and only a rudimentary ovary on the other side. She apparently had no functioning normal ovarian tissue as her FSH tests were strongly positive. Here again, surprisingly, the 17-KS assay preoperatively was not elevated.

A large group of cases of what must still be called idiopathic hirsutism was studied. All the assays were within the normal range with the exception of a few high values. It seems unwise to try to present the data until further studies have been made and until more definite conclusions are forthcoming.

11. Hypothyroidism and hyperthyroidism (table 16). It will be noted that the assays in untreated primary hypothyroidism are always low and sometimes zero. The same findings were present in our one case of hypothyroidism resulting from thyroidectomy where there could be no question that the disease was due to primary thyroid lack (see *case 105*). This test, therefore, occasionally differentiates primary hypothyroidism from that secondary to a panhypopituitarism. However, in our 9 patients with primary hypothyroidism, negative assay results were obtained in only 2 (cases *105*, *108*), and in these never consistently.

The few values on patients with hyperthyroidism are somewhat on the low side, but this may very well be due to secondary non-specific factors, such as malnutrition rather than to a fundamental action of the hormone.

12. Diabetes mellitus (table 17). There is no reason to believe that disorders of the islands of Langerhans should directly have any effect on the 17-KS assay. In table 17 are recorded the findings in 6 cases of diabetes. The values are probably about what one would expect if allowance is made for age, nutrition and infection.

13. Miscellaneous conditions (table 18). In table 18 are recorded some miscellaneous conditions. It will be noted that two non-endocrine dwarfs (cases *120*, *122*) did not have negative values in contrast to the pituitary dwarfs. An achondroplastic dwarf of 15 years (*case 121*) had an assay somewhat above the average. It is of interest that the values were not high during pregnancy inasmuch as there is a hyperplasia of the adrenals at this time. This finding is in agreement with that in acromegaly (vide supra). Following delivery, there is an immediate lowering of 17-KS assays. One of two cases of myasthenia gravis had perfectly normal values; the other had values which were somewhat low. Two cases of functional impotence, as was to be expected, had perfectly normal values. Two young male patients (cases *133* and *134*) with gynecomastia, small testes, and normal secondary sex development excreted on the average 4.7 and

TABLE 17. SIX CASES OF DIABETES MELLITUS

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
114 (38889)	Diabetes mellitus	Female, 67 yr.; known diabetes 15 yr.; 3 operations in past 2 mo. for infection of foot; off insulin at onset, but regulated and wound healing at time of assay; fasting blood sugar occasionally up to 200 mg.%.	2	4.4, 4.7	4.6
115 (229854)	Diabetes mellitus	Male, 53 yr.; diabetes 20 yr.; recovering from urinary infection and 3 operations on gangrenous toe; considerable arteriosclerosis and poor peripheral circulation. Insulin requirement 36 U daily.	2	4.7, 7.7	6.2
116 (239592)	Diabetes mellitus	Negress, 49 yr.; severe diabetes giving symptoms 3 mo.; Hinton +, ? neurosyphilis; required 44 U insulin daily; vomiting and distension following operation for fibromyoma.	2	4.7, 5.0	4.9
117 (239411)	Diabetes Mellitus; obesity	Female, 41 yr.; diabetes 5 yr.; required 35 to 60 U insulin daily; obese.	1	—	7.4
118 (170820)	Diabetes mellitus	Male, 65 yr.; diabetic 1 yr.; insulin requirement 12 to 16 U; toe amputated for infection, healing without complications; urine free of sugar and acetone.	2	4.2, 5.4	4.8
119 (235035)	Diabetes mellitus	Negress, 63 yr.; diabetes 2 yr., controlled satisfactorily by diet; hysterectomy for fibromyomata; post-operative course uneventful.	2	3.8, 4.2	4.0

TABLE 18. 16 MISCELLANEOUS CASES: NON-ENDOCRINE DWARFS (2 CASES), ACHONDROPLASIA (1 CASE), PREGNANCY (3 CASES), MYASTHENIA GRAVIS (2 CASES), FUNCTIONAL IMPOTENCE (2 CASES), FRÖHLICH'S SYNDROME (1 CASE), PRECOCITY PROBABLY OF HYPOTHALAMIC ORIGIN (2 CASES), AND GYNECOMASTIA (3 CASES)

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
120 (*168199*)	Dwarfism, non-endocrine; chronic renal acidosis	Female, 18 yr.; ht. 50″; wt. 72 lb.; dwarfism due to renal disease with chronic acidosis which had produced marked bone disease simulating rickets; sexual development normal.	2	2.4, 3.4	2.9
121 (*156714*)	Achondroplastic dwarf	Female, 15 yr.; one of identical twins with characteristic achondroplasia, ht. 52.3″; span 50″; wt. 105 lb.; menarche at 13 yr., secondary sex development unusually advanced.	1	—	15.1
122 (*23709*)	Dwarfism, non-endocrine	Male, 19 yr.; under observation 5 yr. ago when 14 yr. old; ht. 45.6″; span 50″; wt. 53 lb.; slow growth since 8 yr. old, muscular dwarf with no secondary sex development; bone age markedly retarded, sella normal; received thyroid therapy with very little response. Went through normal puberty 2 yr. ago. At time of 17-KS assay, ht. 50.8″, wt. 68.5 lb., taking 1½ gr. of U.S.P. thyroid daily; I.T.T. normal.	2	1.2, 2.3	1.8
123 (Private patient)	Normal pregnancy	28 yr.; assays every 1 to 2 wk. from 1st to 10th month; 17-KS fell to 7.0 mg. on day after delivery, was 7.2 mg. on 7th and 8.2 mg./24 hr. on 22nd day after delivery.	25	9.1–15.4	11.2
124 (Private patient)	Normal pregnancy	32 yr.; two assays 1 and 2 wk. before delivery.	2	7.0, 8.4	7.7
	Following delivery	Five assays during month after delivery.	5	2.4–6.6	4.0
125 (Private patient)	Normal pregnancy	28 yr.; two assays 1 mo. before delivery. Level fell to 2.2 mg. on day following delivery; rose to 5.6 mg. 5 days later; three assays during next 2 wk. averaged 4.8 mg./24 hr.	2	4.7, 6.8	5.8
126 (*231048*)	Myasthenia gravis	Female, 19 yr.; myasthenia gravis for 1 yr.	2	7.6, 9.3	8.5
127 (*232173*)	Myasthenia gravis	Female, 22 yr.; muscular weakness and fatigability; 2 normal pregnancies, symptoms worse after each; typical neurological signs of myasthenia gravis.	2	2.7, 5.9	4.3
128 (*159232*)	Impotence, functional	Male, 40 yr.; impotence and decrease in libido 2 yr.	2	8.5, 16.4	12.5
129 (Private patient)	Impotence, functional	Male, 50 yr.; decreased libido; had had one child; physically normal.	2	7.5, 12.4	10.0
130 (*163653*)	Fröhlich's syndrome; suprasellar cyst	Female, 18 yr.; no signs puberty and no growth since 13 yr.; bone age retarded. Assays made 10 mo. after removal of suprasellar cyst. FSH still negative at this time and menarche had not occurred. (4 mo. later 2 assays were 5.1 and 5.4 mg./24 hr.)	2	1.4, 1.5	1.5
131 (*227246*)	Hydrocephalus; precocious puberty; obesity; amenorrhea	Female, 11 yr.; hydrocephalus; mental deficiency; precocious puberty at 3 yr.; at 9 yr. convulsions, increasing mental deterioration, obesity, polydipsia, polyuria, and finally amenorrhea; at 11 yr. no catamenia for 2 yr.; bone age and secondary sex characteristics precocious; FSH negative.	2	3.6, 4.0	3.8
132 (*197228*)	Pubertas precox with osteitis fibrosa disseminata, and pathologic pigmentation	Female, 9 yr.; periods since 4½ mo. old; disseminated osteitis fibrosa and areas of pigmentation. (For details of case and syndrome see *case* 3, Albright, Butler, Hampton, and Smith (37).)	2	1.2, 1.5	1.4
133 (*237213*)	Gynecomastia; small testes	Male, 17 yr.; enlargement of breasts 4 yr.; secondary sex development normal; wt. 113 lb.; testes small; bone age slightly retarded; FSH test negative. Bilateral mastectomy performed.	2	4.1, 5.3	4.7

TABLE 18.—*Continued*

Case No. and hospital No.	Diagnosis	Clinical data	No. of assays	Range mg./24 hr.	Average mg./24 hr.
134 (*119837*)	Gynecomastia; small testes	Male, 18 yr.; enlargement of breasts 2 yr.; secondary sex development normal; wt. 111 lb.; ht. 69″; large larynx; normal facial, axillary, perianal and pubic hair; penis and prostate normal; testes very small; FSH test positive. After testosterone propionate 75 mg. per wk. for 2 mo. no obvious change in breasts or testes, weight increased to 118 lb., felt stronger.	2	6.0, 6.5	6.3
135 (*249557*)	Gynecomastia; normal testes	Male, 14 yr.; enlargement of breasts 2.5 yr.; secondary sex development normal for age; wt. 169 lb.; general obesity with abdominal panniculus; fine skin; scant axillary, no facial or pubic hair; high voice; penis normal, testes normal (pre-adolescent); prostate small.	1	3.9	3.9

6.3 mg./24 hr. respectively. A patient with Fröhlich's syndrome (*case 130*) had low but not negative values.

The Effect of Hormone Therapy on 17-Ketosteroid Assay

Testosterone propionate (table 19). It is believed that the 17-KS assay is of value not only in diagnosis but also in following the effect of therapy. In table 19 are shown the results of some 17-KS assays on various patients, both before and after intramuscular administration of testosterone propionate. The results with the panhypopituitary patients with no 17-KS in the urine before treatment probably give the best indication of the excretion of injected testosterone as 17-KS, since in other patients the possibility exists that the injections may alter the body's production of 17-KS. It will be seen that in the neighborhood of 50% of the injected steroid was recovered in the urine as 17-KS. With the eunuchoid patients the recoveries were probably of the same order. These results are in accord with several other reports showing increase of 17-KS excretion following testosterone injections (33, 38). For what indication it may give of the dose of testosterone required for full replacement therapy in eunuchoidism, it may be noted that 25 mg. three times per week resulted in 17-KS assays within the lower range of normal and doses of 25 mg. daily in assays within the upper limits of normal. Some indication of the duration of the effect of these injections is shown by the figures of *case 72*: 11.2 mg. on the day of injection; 9.4 mg. on the next day; and 7.9 mg. on the third day. Large increases in 17-KS excretion occurred in one case of Cushing's syndrome during testosterone administration. The 17-KS assay is also of use in following the effect of pellets of testosterone.

Desoxycorticosterone acetate (table 20). In table 20 are shown results of 17-KS assays before and during desoxycorticosterone acetate therapy in three conditions: pan-hypopituitarism, acromegaly and Addison's disease. A slight rise was found in all three. We would emphasize the slightness of the rise rather than the fact that there was a rise since, as will be seen, such large doses were given that in the patients with Addison's disease and panhypopituitarism, edema was produced. Furthermore, it is by no means certain that even the slight rise was due to an excretion product of desoxycorticosterone acetate.

Chorionic gonadotropin (*synonyms: APL, Pregnancy Prolan, PU*) (table 21). Chorionic gonadotropin was administered in most instances in doses of approximately 1000 international units, 5 times weekly for about 3 weeks. Patients with 4 types of conditions

TABLE 19. EFFECT OF TESTOSTERONE PROPIONATE THERAPY ON 17-KS EXCRETION

Diagnosis	Patient	Range without therapy; mg./24 hr.	Representative values during therapy; mg./24 hr.	Dosage
Panhypopituitarism	*Case 46*, table 11	<0.5 (3 assays)	5.8 8.1	25 mg. 3×weekly
Panhypopituitarism; or Eunuchoidism with negative FSH	*Case 47*, table 11	<0.5 (2 assays)	5.4	25 mg. 3×weekly
Eunuchoidism with negative FSH	*Case 70*, table 13	6.4–6.4 (2 assays)	10.8 14.6 17.2	25 mg. 3×weekly
			12.0	2 pellets, 150 mg. each
Eunuchoidism with negative FSH	*Case 71*, table 13	2.6–3.3 (2 assays)	7.8 4.5 12.0	25 mg. 3×weekly
			6.1	2 pellets, 150 mg. each
Eunuchoidism with negative FSH	*Case 72*, table 13	4.2–5.4 (2 assays)	9.3 11.3 10.1	25 mg. 3×weekly. 2 pellets, 150 mg. each
Eunuchoidism with negative FSH	*Case 74*, table 13	1.5–2.3 (3 assays)	7.7 5.7 5.9	25 mg. 3×weekly
			4.2	2 pellets, 150 mg. each
Eunuchoidism with negative FSH	*Case 76*, table 13	3.2–4.6 (4 assays)	6.3 9.8 13.1	25 mg. 3×weekly
			9.7	2 pellets, 150 mg. each
Eunuchoidism with positive FSH	*Case 68*, table 13	6.7–9.6 (5 assays)	8.5 17.0 19.8	25 mg. 3×weekly
			10.4	1 pellet, 150 mg.

TABLE 20. EFFECT OF DESOXYCORTICOSTERONE ACETATE THERAPY ON 17-KS EXCRETION

Diagnosis	Patient	Range without therapy; mg./24 hr.	Values during and after therapy; mg./24 hr.	Therapy	Clinical observations
Panhypopituitarism	*Case* 46, table 11	<0.5 (3 assays)	<0.5 (12 assays; determined daily until day after last injection)	5 mg dy.[1] for 4 d. 10 mg. dy. for 2 d. 30 mg. dy. for 5 d.	Edema developed on 3rd day after cessation of therapy
Panhypopituitarism	*Case* 49, table 11	<0.5 (3 assays)	<0.5 (1st d.) 1.0 (3rd d.) 0.5 (4th d.) <0.5 (5th d.)	2.5 mg. dy. for 2 d. 5 mg. dy. for 2 d. 10 mg. dy. for 1 d.	Edema developed on 4th day
Panhypopituitarism	*Case* 51, table 11	<0.5 (4 assays)	1.7 (1st d.) 0.8 (4th d.) <0.5 (5th, 6th and 7th d.) 0.6 (9th d.) <0.5 (several subsequent assays during therapy)	5 mg. 1st and 2nd d. 2.5 mg. 6th and 7th d. 5 mg. dy. from 9th d.	—
Acromegaly	*Case* 58, table 12	3.6–6.0 (4 assays)	8.7 (1st d.) 6.6 (2nd d.) 5.9 (3rd d.) 7.4 (4th d.) 6.0 (5th d.) 8.2 (6th d.) 7.6 (9th d.) 6.4 (11th d.)	5 mg. 1st and 2nd d. 10 mg. 3rd and 4th d. 20 mg. 5th and 6th d.	No clinical effect
Addison's disease, (male)	*Case* 31, table 9	1.3–1.8 3.0 3.9		6 pellets of approximately 100 mg. each	—
Addison's disease, (female)	*Case* 29, table 9	<0.5 (6 assays)	<0.5 (5 assays)	5 mg. dy. for several weeks	—
Addison's disease, (female)	*Case* 26, table 9	<0.5 (4 assays)	<0.5 (5 assays)	5 mg. dy. for several weeks	—
Addison's disease, (female)	*Case* 27, table 9	<0.5 (3 assays)	1.2 (4th d.) <0.5 (7th, 8th, 10th and 25th d.)	10 mg. 1st d. 15 mg. 2nd d. 20 mg. 3rd to 10th d. 4 pellets of approximately 125 mg. each inserted on 11th d.	Edema developed on 8th day

[1] d., day(s); dy., daily.

received it: male panhypopituitarism, male castrates, 'eunuchoidism-with-negative-FSH,' and 'eunuchoidism-with-positive-FSH.' In the first group there was a definite though small response, first measurable within 5 days (table 21, cases 53, 46, 47). There was no rise in the male castrate patient (*case* 66). Of six eunuchoid patients with negative FSH test results (sases 70, 71, 72, 74, 76, 77, table 21), the 17-KS excretion showed a definite increase in all but two cases, 71 and 74. Both of these cases had received APL therapy on a previous occasion and it is possible that antibodies had been developed to this particular preparation. *Case* 77, however, showed an equally marked rise with a second course of APL therapy. Thus, with the first course the assays rose from 3.9 and 3.0 mg./24 hr. to 9.2 and 8.4 mg./24 hr.; with the second course, after an interval of three months without therapy, the assays rose from 3.5 and 3.8 mg./24 hr. to 10.1 and 8.1 mg./24 hr. Neither of the two cases of 'eunuchoidism-with-positive-FSH' (cases 67 and 68, table 21) showed a rise following APL therapy. These findings, therfore, support the assumptions that chorionic gonadotropin stimulates the male gonads to produce an increased amount of 17-ketosteroids or their precursors, that chorionic gonadotropin has no effect on the 17-ketosteroid production by the adrenal cortex, and that the group of eunuchoid patients with negative FSH tests are not suffering from primarily gonadal underfunction.

SUMMARY AND CONCLUSIONS

1) The results are submitted of over 1500 urinary 17-ketosteroid (17-KS) assays by the method of Callow on a series of patients suffering from various endocrine and related disorders.

2) A method is presented which, it is believed, partially corrects the errors resulting from the color produced by non-17-ketosteroids; with this method zero assays (i.e. <0.5 mg. of sterone/24 hr.) were ob-

TABLE 21. EFFECT OF CHORIONIC GONADOTROPIN THERAPY ON 17-KS EXCRETION

Diagnosis	Patient	Range before therapy mg./24 hr.	Values during and after therapy; duration of therapy; number of injections of 1000 I. U. of APL; mg./24 hr.	Clinical observations
Panhypopituitarism; dwarfism	*Case* 53, table 11	<0.5 (6 assays)	1.0 (5 d.[1], 3 inj.) 1.4 (18 d., 12 inj.)	No clinical response
Panhypopituitarism	*Case* 46, table 11	<0.5 (3 assays)	1.2 (8 d., 5 inj.) 2.4 (10 d., 8 inj.) 1.1 (11 d., 9 inj.)	No clinical response
Panhypopituitarism; or eunuchoidism with negative FSH	*Case* 47, table 11	<0.5 (2 assays)	<0.5 (14 d., 13 inj.) 1.4 (15 d., 14 inj.) 1.8 (20 d., 19 inj.) 1.8 (21 d., 20 inj.)	No clinical response
Eunuchoidism with negative FSH	*Case* 70, table 13	6.4–6.4 (2 assays)	12.4 (11 d., 10 inj.) 8.4 (20 d., 18 inj.) 7.4 (29 d., 25 inj.) 8.5 (34 d., 29 inj.)	No clinical response
Eunuchoidism with negative FSH	*Case* 71, table 13	2.6–3.3 (2 assays)	3.8 (7 d., 5 inj.) 2.3 (13 d., 10 inj.) 3.7 (20 d., 15 inj.) 4.5 (30 d., 23 inj.) 4.8 (34 d., 25 inj.)	No clinical response
Eunuchoidism with negative FSH	*Case* 72, table 13	4.2–5.4 (2 assays)	7.0 (1 d., 1 inj.) 8.1 (14 d., 11 inj.) 5.0 (15 d., 12 inj.) 7.2 (19 d., 17 inj.)	Testes enlarged, no other change
Eunuchoidism with negative FSH	*Case* 74, table 13	1.5–2.3 (3 assays)	1.0 (5 d., 5 inj.) 2.6 (10 d., 9 inj.) 2.1 (14 d., 12 inj.) 2.4 (26 d., 24 inj.)	Testes enlarged, no other change
Eunuchoidism with negative FSH	*Case* 76, table 13	3.2–4.6 (4 assays)	7.9 (14 d., 10 inj.) 7.2 (26 d., 20 inj.)	Slight virilizing effect
Eunuchoidism with negative FSH	*Case* 77, table 13	3.0–3.9 (2 assays)	9.2 (22 d., 18 inj.) 8.4 (23 d., 18 inj.)	Slight increase in libido
Eunuchoidism with positive FSH	*Case* 67, table 13	8.1–9.0 (4 assays)	8.1 (19 d., 16 inj.) 6.0 (20 d., 16 inj.)	No clinical effect
Eunuchoidism with positive FSH	*Case* 68, table 13	6.7–9.6 (5 assays)	7.4 (17 d., 15 inj.) 4.8 (22 d., 18 inj.) 4.8 (30 d., 23 inj.)	No clinical effect
Male Castrate	*Case* 66, table 13	2.3–3.6 (4 assays)	3.5 (20 d., 20 inj.) 2.3 (21 d., 21 inj.)	No clinical effect

[1] d, days.

tained in conditions where other procedures yield merely very low assays.

3) The data indicate that the method is accurate to approximately 10 to 20% (1 to 2 mg. of sterone/24 hr.); that on the average 89% of added sterone can be recovered; and that urinary samples are adequately preserved in the icebox with 10 cc. concentrated hydrochloric acid per liter for a few weeks before extraction.

4) The range for 17-KS excretion in a small series of normal males, between the ages of 20 and 40, was 8.1 to 22.6 mg. with an average of 13.8 mg. of sterone/24 hr. and in a similar series of females, 5.1 to 14.2 mg. with an average of 9.0 mg. of sterone/24 hr. The assays were found considerably decreased in old age.

5) The 17-KS excretion appears to be lowered by many non-endocrine conditions, notably malnutrition, various gastrointestinal diseases, anemia, infection, etc. Liver disease seems to have a special predisposition in this respect.

6) The results of assays on endocrine cases were consistent with the hypothesis that all the urinary 17-ketosteroids are derived from the male gonads and the adrenal cortex, about 9 mg. in round numbers coming from the adrenal cortex and about 5 mg. from the male gonads. Thus in the conditions listed below, when uncomplicated, the assays actually found approximated the following hypothetical values.

	mg.
a) Normal male	14.0
b) Normal female	9.0
c) Female with Addison's disease	0.0
d) Male with Addison's disease	5.0
e) Panhypopituitarism (either sex)	0.0
f) Gonadectomized male	9.0
g) Gonadectomized female	9.0

7) Five female patients with Addison's disease all had zero assays (less than 0.5 mg./24 hr.); this evidence supports the hypothesis that all the urinary 17-ketosteroids in the female originate from the adrenal cortex.

8) Patients with panhypopituitarism (i.e. underfunction of all elements of anterior pituitary) had zero assays (13 cases) or very low assays (2 cases). It is believed that this test may help in separating such patients from those with anorexia nervosa in which the values may be normal, or low, but as yet not zero in any case.

9) Certain conditions, notably pregnancy and acromegaly (6 cases), known to be associated with hyperplasia of the adrenal cortex (probably compensatory) had normal or low 17-KS assays.

10) Patients with the adreno-genital syndrome due to adrenal tumor or adrenal hyperplasia have been found to have very high assays.

11) Female patients with precocity due to probably hypothalamic lesions do not have an increased 17-KS excretion.

12) Of five patients with Cushing's syndrome, two with adrenal cancer had very high 17-KS assays; three without adrenal tumors had either high or high normal assays in spite of their debility. It is believed that this is evidence that Cushing's disease is due to a hyperadrenocorticism.

13) One patient with virilism due to an arrhenoblastoma had a 17-KS assay within normal limits as did one patient with virilism due to a disgerminoma.

14) Twelve cases of male eunuchoidism were studied. These are divided into two groups, those with positive follicle stimulating hormone (FSH) test results in the urine and those with negative FSH test results. The cases in the latter group differ from gonadectomized males not only in having no increase of FSH in the urine but also in exhibiting a 17-KS assay rise with chorionic gonadotropin therapy. In this eunuchoid group with negative FSH test results, furthermore, the average 17-KS excretions varied between 2.8 and 6.4 mg./24 hr. and were thus considerably lower than is to be expected in uncomplicated male hypogonadism. It is, therefore, believed that this syndrome is of pituitary origin and that the production of 17-KS by the adrenal cortex is likewise impaired.

15) The 17-KS excretion in hypothyroidism is very low, and in rare instances less than 0.5 mg./24 hr.

16) About 50% of testosterone propionate injected intramuscularly is recoverable as 17-KS in the urine.

17) Chorionic gonadotropin therapy increases 17-KS excretion by stimulation of the testis but not by stimulation of the adrenal cortex; thus it produces no rise in the 17-KS excretion in male castrates and in eunuchoid patients with positive FSH test results, but does produce a rise in panhypopituitarism in males and in eunuchoid patients with negative FSH test results.

18) Desoxycorticosterone acetate therapy increases very slightly the 17-KS excretion in patients with panhypopituitarism and in female patients with Addison's disease.

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ANOREXIA NERVOSA

ENDOCRINE FACTORS IN UNDERNUTRITION[1]

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IN 1874 SIR WILLIAM GULL (1) described two young women in whom anorexia led to starvation and "depression of all vital functions," with bradycardia, amenorrhea, and the appearance of ageing. Recovery occurred when the caloric intake was increased. Since Gull called attention to this syndrome, many other cases of so-called anorexia nervosa have been described. In 1930 Berkman (2) reported 117 cases which had been observed at the Mayo Clinic between 1917 and 1929. In 1936 Ryle (3) reported 51 cases. The syndrome, observed most frequently in young women, is characterized by anorexia, usually associated with psychic disturbances, and followed by marked weight loss, hypotension, bradycardia, subnormal temperature, lowered basal metabolic rate, atrophy of the genitalia, amenorrhea, hypoglycemia, increased glucose tolerance, and occasionally loss of hair and the appearance of senility. During recent years the similarity of this clinical syndrome to that of hypophyseal cachexia (Simmonds' disease) has been the subject of frequent comment (4–9). Without direct evidence of a destructive lesion of the anterior lobe of the hypophysis, there appears to be no certain means of differentiating between anorexia nervosa and Simmonds' disease. It has been suggested that the latter diagnosis should not be made clinically unless anorexia nervosa can be ruled out by appropriate psychiatric study or by failure to respond to the therapeutic test of increasing the caloric intake. Extreme emaciation, appearance of ageing, atrophy of breasts, loss of hair, amenorrhea with loss of sexual function and loss of secondary sex characteristics have been said to favor the diagnosis of Simmonds' disease. However, all of these have been noted in patients with anorexia nervosa.

The prominence of changes in metabolism, gonads, and sexual function in patients with anorexia nervosa and the similarity of the syndrome as a whole to that of anterior pituitary insufficiency has led to much speculation as to the role played by the endocrine system in such patients. Most observers are agreed that the various manifestations of the syndrome are in some way due to the malnutrition and emaciation. The occasional presence of preexisting menstrual disturbances has suggested that there may have been an underlying ovarian or pituitary disturbance in some cases (5, 8, 10). Leede (11) considered the condition "pluriglandular" in origin and felt that suprarenal insufficiency played the most important role. Levi (12) attributed the entire picture to thyroid deficiency. Sheldon (10) regarded anorexia nervosa as "functional Simmonds' disease" or "pituitary black-out of psychological origin." As a result of further studies (13), in particular of the carbohydrate metabolism, he modified this view and concluded there was no reason to invoke an endocrine factor. Bruckner, Weis and Lavietes (4) state "it seems possible that these changes (in metabolism, gonads and carbohydrate tolerance) in malnutrition represent a mechanism for conservation mediated through the pituitary, but there is no objective evidence to support this hypothesis." Farquharson and Hyland (5) expressed the belief that "this metabolic disorder is based primarily on psychologic disturbance and that its various manifestations should not be attributed to dysfunction of any endocrine gland." Richardson (6, 8) emphasizes the fact that the undernutrition resulting from starvation of psychogenic origin produces the same effects on metabolism and the endocrine system as destruction of the anterior lobe of the hypophysis. Sevringhaus (14), in commenting on anorexia nervosa, asks: "Does prolonged inanition lead to hypo-function of the anterior pituitary and thereby cause the amenorrhea, hypotension, asthenia, etc., or does such pathologic inability to eat occur only in individuals with an inadequately functioning pituitary?" Van Balen (9) feels that the clinical picture which is specified as Simmonds' cachexia is the same whether described under the name of hypophyseal or endogenous emaciation. Berkman (2) and Kylin (15) suggest that anorexia nervosa should be regarded as an independent clinical entity.

The course of the disease and the frequency of recovery when food intake is increased, with or without

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other treatment, indicate that the undernutrition, resulting from anorexia of psychic origin, is of primary etiologic significance. A review of the recent literature suggests that the effect of undernutrition on the endocrine system has not been adequately explored as a possible explanation of many of the abnormalities in anorexia nervosa which appear to be of endocrine origin. It is the purpose of this communication to report three additional cases of anorexia nervosa and to review some of the experimental and clinical evidence bearing on the effect of inanition on the endocrine glands.

CASE REPORTS

Case 1. F. M., a 16-year-old boy was admitted to the hospital on Oct. 26, 1937, with complaint of weight loss. One year before, when he weighed 140 lb. he was considered to be somewhat overweight and was called "Fatty" by his playmates. He resented this appellation, refused to allow his mother to butter his sandwiches and began to direct her in the preparation of meals, lest their caloric content be too high. In August, 1937, he accused his mother of attempting to increase his weight and began to limit his diet more sharply than before. He became overaffectionate toward his mother, became very solicitious of her diet and often attempted to force her to eat a second meal immediately after a full meal. He became irritable, depressed and weak, and sometimes entertained ideas of suicide. He frequently expressed a desire to gain weight but refused to eat. An analysis of his diet for several weeks before admission to the hospital indicated that the daily caloric intake was about 400 calories, mainly in fruits and vegetables. He had lost from his previous weight of 140 lb. to about 100 lb. There had been no vomiting or other gastrointestinal symptoms. For several months he had been intolerant of cold and had spent most of the day huddled over the radiator.

His development during childhood had been normal and he had had no previous illnesses. He had always been shy and reticent and had manifested no interest in the opposite sex.

On physical examination the patient was an emaciated boy of 16 who looked somewhat older than his given age. His weight was 45.8 kg. All bony landmarks were prominent. The skin was dry and rough; the hands and feet were dry, rough, cold and bluish-red in color. The thyroid was not palpable. The lungs were clear. The heart sounds were distant. The pulse rate was 36 per minute. The blood pressure was 86 systolic, 70 diastolic in the supine position, 72 systolic, 50 diastolic standing. The penis and testes were of approximately normal size. The prostate was markedly atrophic and could not be identified with certainty. Hair was of normal texture and distribution except that the crines pubis was distinctly of the female type. His behavior was somewhat negativistic; he was temperamental, impulsive and irritable. There were no hallucinations. There was no evidence of mental retardation and the flow of speech was approximately normal. His intelligence was considered above normal. His mental age (revised Binet) was 15 years. I.Q. was 106. At times he ran

Fig. 1. *Case 1. F. M.* Left, December 9, 1937. Right, December 27, 1938.

up and down the halls of the division in an attempt to get warm.

Laboratory findings were as follows: red blood cells, 4,300,000; hemoglobin, 13.1 gm. per 100 cc.; white blood cells, 5,200. The red blood cells were normal in size and shape and platelets were present in normal numbers. The differential count was as follows: neutrophils, 44%; lymphocytes, 52%; monocytes, 4%. The blood Wassermann reaction was negative. The urinalysis showed no abnormalities, except a trace of acetone. The stool was normal. The blood non-protein nitrogen was 44 mg.%; uric acid, 4.7 mg.%; serum chloride, 93 m.eq. per l.; carbon dioxide combining power, 50 vol.%; total serum protein, 6.7 gm.%; serum albumen, 4.7 gm.%; serum globulin, 2.0 gm.%; cholesterol, 165 mg.%; serum calcium, 9.3 mg.%; phosphorus, 2.8 mg.%. Sugar tolerance curves were as follows: fasting blood sugar, 63 mg.%; ½ hour after 50 gm. of glucose by mouth, 76; 1 hour, 89; 2 hours, 83; 3 hours, 54; 4 hours, 57. Fasting blood sugar 68 mg.%; 15 minutes after 25 gm. of glucose intravenously, 152; 30 minutes, 91; 1 hour, 82; 2 hours, 37; 3 hours, 47. The result of an insulin tolerance test was as follows; fasting blood sugar, 56 mg.%; 15 minutes after 3 U of insulin intravenously, 39; 30 minutes, 22; 1 hour, 22; 1½ hour, 24. During the period between 30 and 90 minutes after the intravenous administration of insulin the patient was pale, perspiring, dizzy and confused. These symptoms were promptly relieved by the administration of glucose. The circulation time was 22 seconds (Decholin method). The electrocardiograph showed a P-R interval of 0.20 seconds; there was bradycardia of 35 per minute with sinus rhythm. The basal metabolic rate was −39%; repeated, −42%. X-rays of the skull showed a normal sella turcica

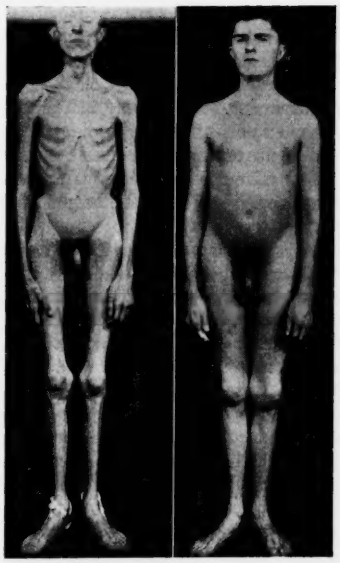

Fig. 2. *Case 2.* C. Left, December 6, 1938. Right, March 27, 1939.

shadow. The visual fields were normal. X-ray of the chest showed a small cardiac shadow but there were no pulmonary abnormalities. X-ray examination result of the gastrointestinal tract was negative except for generalized depression in tone.

The rectal temperature varied between 34.5°C. and 36.5°C., the pulse rate varied between 32 and 50 and was usually below 40 per minute. During a period of two weeks, attempts to encourage the patient to eat were unsuccessful; food was hidden or disposed of in various ways. His weight decreased from 45.8 to 41.2 kg. during the first few days in the hospital (fig. 1). Tube feeding was resorted to, and a caloric intake of approximately 2,000 calories was achieved by supplementing the oral intake with tube feeding. At the end of a month the weight had increased to 48 kg.; he was somewhat more cooperative but there was no other essential change in his condition. The B.M.R. was −41%; the pulse rate and temperature were unchanged. Attempts to care for the patient at home were unsuccessful. After several abortive attempts to run away, he was returned to the psychiatric division and a series of attempts was made to influence the picture with endocrine therapy. The administration of small amounts of insulin before meals and the addition of liver extract intramuscularly and of vitamin supplements to the diet had no effect. Successive courses of an anterior pituitary extract, an anterior pituitary-like extract of pregnancy urine and a combination of the latter and of a pituitary extract containing 'growth complex' were without effect.

During the latter part of August, 1938, the patient was again allowed to return home. On the first of September he weighed 42.6 kg. The rectal temperature was 34.0°C.; the pulse rate was 36 per minute. The blood pressure was 80 systolic, 60 diastolic. The B.M.R. was −56%; repeated, −51%. The administration of desiccated thyroid, U.S.P., in doses of 0.016 gm. daily was begun; after two weeks the dosage was increased to 0.016 gm. twice daily. At about this time the patient abruptly developed a desire to eat, took an interest in family and social affairs and returned to school at his own request. On September 27, the weight was 50.4 kg., the pulse 84, the temperature 36.5°C. He had failed to keep an appointment the week before because of a gastrointestinal upset precipitated by overeating. His mother had noted a marked change in his personality. He was more tractable and agreeable and had again shown an interest in his musical instrument after a period of a year of disinterest.

The patient was again seen on Nov. 22, 1938. He had continued to gain weight and had a voracious appetite. He was well adjusted socially, at home and at school. He had a normal tolerance to cold and remarked that he was perspiring for the first time in many months. He was having nocturnal penile erections; these had been absent during his illness. The temperature was 36.6°C., the pulse rate 76 per minute. The blood pressure was 102 systolic, 64 diastolic. Weight was 74.5 kg. He appeared to be somewhat overweight, the face was full and the musculature well developed (fig. 1). The skin was moist and of good turgor. The penis and testicles seemed larger than before. The prostate, which previously could not be identified, was easily palpable and seemed to be of about normal size. The B.M.R. was −2% on October 31. Immediately thereafter the patient discontinued the thyroid, which had been continued in a dosage of 0.016 gm. twice daily. On December 30th the B.M.R. was −19%. On the same day the sugar tolerance curve was as follows: fasting blood sugar 87 mg.%; ½ hour after 50 gm. of glucose, 80 mg.%; 1 hour, 114; 2 hours, 91; 3 hours, 70.

Attempts to follow this patient have been unsuccessful because of his refusal to return to the clinic, but his mother recently reported that he has remained in good health.

Case 2. J. C., a 20-year-old single man, was admitted to the hospital on December 2, 1938. He had never been well. At the age of 12 he was badly frightened as a result of an automobile accident and his family felt that he had never recovered from this. At the age of 14 he had mastoiditis, with operation, sinus thrombosis and jugular ligation. He was in such poor physical condition that most of the surgery was done without anesthesia. He gradually recovered from this illness and gained weight slowly to a maximum of 125 lb. About 6 months before admission to the hospital, while a sophomore in college he became worried because of poor marks and his appetite began to fail. This progressed to marked distaste for food and occasional nausea and vomiting appeared. In May, 1938, he had come home from school because of illness and since that time had eaten very little in spite of attempts of the family to encourage him. He complained of a lump in his throat after taking a small amount of food and refused to continue with meals. During the past year he had lost in weight from 125 to 69 lb. During the week before admission to the hospital he had become so weak that he was forced to take to his bed. There had been symptoms of decreased heat production and some loss of hair. As far as could be learned from the patient and his family, there had been no other symp-

toms. He later stated that during the six months before admission to the hospital there had been complete suppression of sexual desire and loss of ability to have penile erections.

Physical examination showed a markedly emaciated young man weighing 33 kg. (fig. 2). All bony landmarks were prominent. He appeared older than his given age. The skin was dry and rough. Axillary and pubic hair was scanty; There was no body hair. The beard was sparse. The thyroid was not palpable. The lungs were clear. The heart showed no abnormalities. Blood pressure was 104 systolic, 72 diastolic. The prostate was so small that it could not be identified. Psychiatric note by Dr. William Mathews was as follows.

The patient was bedridden because of weakness, and presented the picture of marked emaciation. Speech was slow and soft, understandable only with close attention. His speech resembled that of a man of perhaps 60 or 70. He replied to questions in an intelligent and coherent manner, but did not converse beyond replying to questions. He stated that he felt quite well and had no complaints except that of weakness. He accepted hospitalization on the psychiatric division and expressed the desire to get well. When asked why he did not eat he replied that he had no appetite or desire for food and therefore would not eat. He denied having any pain, discomfort or other symptoms. He seemed to resent inquiry into bowel habits. There was little evidence of emotional reaction and he exhibited lack of interest in contrast to previous active interests. He denied being sad, happy, worried, anxious or perplexed but said that he could not understand the matter of no desire to eat. There were no misinterpretations, delusions, or hallucinations. There were no compulsion phenomena. He was well oriented and memory was excellent. There was a good grasp of general information. Calculations were done slowly but correctly. He realized the need for medical care, appreciated the fact that his weight loss was due to loss of appetite and thought that his illness might be of a mental nature. His judgment seemed good except in the matter of voluntary starvation to which he was submitting himself.

Laboratory observations were as follows: red blood cells, 4,600,000; hemoglobin, 14.6 gm.; white blood cells, 7,700. The differential count showed eosinophils, 1%; neutrophils, 67%; lymphocytes, 24%; monocytes, 8%. A few days later, after correction of dehydration, blood counts were as follows: red blood cells, 2,790,000; hemoglobin, 7.7 gm.; white blood cells, 4,050. Platelets were unusually abundant. The differential count at this time was as follows: basophils, 3%; neutrophils, 71%; lymphocytes 19%; monocytes, 5%. The urine showed no abnormalities. The blood Wassermann reaction result was negative. The blood non-protein nitrogen was 45 mg.%; blood cholesterol, 227 mg.%; serum calcium, 8.9 mg.%; serum phosphorus, 1.6 mg.%; serum albumen, 3.7 gm.%; serum globulin, 1.2 gm.%; serum chloride, 90 m.eq. per l.; blood ascorbic acid, 0.93 mg.%. Sugar tolerance curve was as follows: fasting blood sugar, 64 mg.%; ½ hour after 50 gm. of glucose by mouth, 76; 1 hour, 74; 2 hours, 67; 3 hours, 71. Fluoroscopy of the chest and x-ray examination of the gastrointestinal tract showed no abnormalities. X-ray examination of the skull showed a normal sella turcica. The basal metabolic rate was −20%.

The patient was unwilling to take food by mouth except in small quantities and it was necessary to resort to tube feeding. On December 21 he was put on a liquid formula providing 2,500 calories per day. A week later blood chemistry was as follows: blood non-protein nitrogen, 27 mg.%; fasting blood sugar, 71 mg.%; serum calcium, 10.9 mg.%; phosphorus, 4.6 mg.%; serum albumen, 4.0 gm.%; serum globulin, 1.7 gm.%; icterus index, 7; carbon dioxide combining power, 61 vol.%.

The caloric intake was gradually increased and tube feeding continued until the patient voluntarily ate a full diet. A gradual increase in weight occurred. On March 28th the sugar tolerance curve was as follows: fasting blood sugar, 90 mg.%; ½ hour after 50 gm. of glucose by mouth, 134; 1 hour, 103; 2 hours, 78; 3 hours, 88; 4 hours, 78; 5 hours, 83. On March 29 the B.M.R. was +12%. As he gained weight, he improved mentally and physically. He took an interest in various activities on the division and engaged in occupational therapy and games. On April 11, 1939 he weighed 73 kg. (fig. 2). The blood pressure was 135 systolic, 83 diastolic. The prostate, which previously could not be felt, was easily palpable, rounded and elastic, and seemed to be of about normal size. Blood counts were as follows: red blood cells, 3,990,000; hemoglobin, 11.4 gm.; white blood cells, 5,100. This patient has been followed at intervals and has remained in good health.

Case 3. A. H., a 40-year-old single farmer was admitted to the hospital in November, 1936, with complaints of weakness, nausea and vomiting. He was said to have been in delicate health all his life. In 1922 he had had an appendectomy, followed by influenza. Since that time he had never been well and had complained intermittently of weakness, anorexia, and nausea. He had always been concerned about the opinions his relatives and neighbors held of him, had always lacked initiative and for many years had worked without salary on his brother's farm. During the previous two years he had had frequent headaches accompanied by nausea and vomiting, with increasing anorexia and loss in weight from 150 to 100 lb. On physical examination the weight was 44.6 kg. The patient was

Fig. 3. *Case 3. A. H.* Left, September 12, 1938. Right, May 15, 1939.

described as weak, emaciated, and of elderly appearance. The teeth had been extracted and had not been replaced by dentures. The lungs were clear. The heart and abdomen showed no abnormalities. The blood pressure was 90 systolic, 60 diastolic. The prostate was small and fibrous. There was a small hydrocele. Red blood cells numbered 3,810,000; hemoglobin, 11 gm.; white blood cells, 8,000. The differential count was normal. Urine and stool showed no abnormalities. The blood Wassermann reaction result was negative. The blood non-protein nitrogen was 43 mg.%; serum protein, 5.4 gm.%; serum chloride, 88 m.eq. per l.: serum calcium, 10.4 mg.%; phosphorus, 4.1 mg.%; fasting blood sugar, 89 mg.%. X-ray examination of chest and of the gastrointestinal tract showed no abnormalities. The administration of sodium chloride was followed by return of the serum chloride to normal. Attempts to precipitate an Addisonian crisis by limitation of sodium chloride were unsuccessful. During a stay of 2 weeks in the hospital, his symptoms disappeared and he gained 5 kg. in weight.

After discharge from the hospital, he gained in weight to 60 kg. About May 1, 1937, headache, dizziness, anorexia, nausea and vomiting returned and on May 23 he was re-admitted to the hospital, weighing 45.5 kg. The physical findings were essentially as previously described. Blood pressure was 80 systolic, 60 diastolic. Serum chloride was 92 m.eq. per l. Other laboratory findings were approximately as on the previous admission. During a period of 9 days in the hospital he gained from 45 to 52 kg.

On September 7, 1938, he was admitted to the hospital for the third time. He had done well at home until April, 1938, when he weighed 59 kg. At this time anorexia, nausea, vomiting and weakness returned. Necessity for shaving decreased to twice a week. There had been no evidence of sexual desire or penile erection during the past 2 years. By September, 1938, the weight had decreased to 34.2 kg. The temperature was 35.5°C.; the pulse rate was 54 per minute. The patient was extremely emaciated, looked considerably older than his age of 42 years (fig. 3). The skin was dry, cold and rough. There was no pigmentation of the skin or mucous membranes. The hair was scanty but of normal distribution. The blood pressure was 64 systolic, 28 diastolic. The prostate was so small that it could not be identified with certainty.

Laboratory findings were as follows: red blood cells, 2,560,000; hemoglobin, 7.9 gm. per 100 cc.; white blood cells, 6,500. The differential count was normal. Urinalysis showed no abnormalities. B.M.R. determinations were −8%, −15%. but were not entirely satisfactory. Sugar tolerance curve was as follows: fasting blood sugar, 73 mg.%; ½ hour after 50 gm. glucose by mouth, 83 mg.%; 1 hour, 77; 2 hours, 86; 3 hours, 86; 4 hours, 104. Skull films showed a normal sella turcica shadow. He was given a high vitamin, high calorie diet, and again gained about 5 kg. during his stay in the hospital. From September, 1938 to February, 1939, the patient was followed in the Out-Patient Department and received a course of injections of anterior pituitary-like principle of pregnancy urine. During this time his weight remained stationary at 47 to 48 kg. He was again admitted to the hospital for a period of forced feeding. He consumed a diet of 3,800 to to 4,500 calories and steadily gained in weight. On May 18, 1939 he weighed 60.2 kg. (fig. 3). The blood pressure was 115 systolic, 74 diastolic. The prostate had increased in size. The red blood cell count had increased to 4,170,000, hemoglobin to 11.4 gm. The B.M.R. was +14%.

DISCUSSION

In each of the 3 cases described above, a diagnosis of Simmonds' disease had been seriously considered at some time but was eventually discarded in favor of one of anorexia nervosa. In each instance the latter diagnosis was considered to be confirmed by the response to therapy. The first patient received a number of glandular products over a period of a year without benefit. Improvement in his case began shortly after the administration of a small amount of thyroid substance but at about the same time there was striking change in his personality and increase in appetite and food intake. The second patient made a satisfactory recovery without the administration of any drugs or endocrine products. The third patient received the anterior pituitary-like principle of pregnancy urine without benefit, but improved when the caloric intake was sufficiently increased. It is apparent that in these three patients endocrine therapy, with the possible exception of thyroid in the first patient, was of no benefit, but that striking improvement followed correction of the inanition.

It is of some interest that none of the patients described in this report showed any gross evidence of the recognized vitamin deficiency states or of the protein deficiency edema sometimes seen in malnutrition. Bruckner, Weis and Lavietes (4) attribute the absence of these specific deficiencies in anorexia nervosa to the fact that reduced energy requirements are largely satisfied by the body tissues, which are complete foods, and to the low level of metabolism which diminishes the requirement for vitamins. In two of our patients (*J. C.* and *A. H*) a moderate degree of anemia was observed; the anemia was corrected by the administration of a full diet without extra iron or liver preparations. In these 2 patients, balance studies of electrolyte, protein and mineral metabolism during periods of gain in weight have been made by Drs. Samuel Bassett and E. H. Keutmann and will be reported elsewhere.

The recent literature contains several excellent clinical discussions dealing with the physical and psychiatric aspects of anorexia nervosa and its differential diagnosis and treatment (4, 5, 6, 8, 16). The present discussion will be limited to a consideration of some of the clinical and experimental observations dealing with the effect of undernutrition on the endocrine glands, particularly in relation to the symptomatology of anorexia nervosa, illustrated in the case histories summarized above.

The literature contains only a few references to pathological studies in anorexia nervosa. In some of the earlier cases (17, 18, 19), detailed studies of the endocrine glands were not made. Meyers (20) has described in detail the morphological changes in a patient with prolonged inanition. The patient was a man who had refused food for 60 days and at the time of death weighed 80 lb., having lost about 40% of his body weight. There was marked emaciation. The skin was dry and rough. The body fat had almost entirely disappeared. The adrenal glands showed marked atrophy, and degenerative changes in the cortical cells. The hypophysis showed reduction and degeneration of epithelial cells but some degree of chromatophilia was still present. The thyroid epithelium was very low, with acini distended with colloid; the picture was that of "atrophy and exhaustion," without any evidence of epithelial proliferation. Kylin (15) has described the postmortem findings in two patients with anorexia nervosa. In his first case the hypophysis was reduced to about half normal size and showed a decrease in the number of basophilic cells. The ovaries and adrenals were small. The thyroid follicles were lined by a single layer of flat epithelial cells and were filled with hard colloid. In the second patient the hypophysis was reduced to one-third of its normal weight. The anterior pituitary was composed principally of chromophobe cells; the eosinophilic cells were markedly reduced and showed hyaline changes. The ovaries were small and contained no follicles or corpora lutea. The uterus and adrenals were small. In a recent paper, Richardson (8) reports the case of a 16-year-old girl with anorexia nervosa complicated by terminal pyelonephritis. At autopsy the pituitary was considered normal, except that the eosinophilic cells were small and poorly granulated. The uterus was small. The ovaries were underdeveloped, contained much fibrous tissue and only one medium-sized follicle was seen. The thyroid was considered normal.

Many of the physiologic disturbances occurring in anorexia nervosa were reproduced in the athletes subjected to experimental undernutrition by Benedict and his associates (21). Benedict's studies grew out of mass observations of the effect of lowered rations during the first World War. His experiments were carried out with a selected group of normal, young individuals whose body weights were lowered as a result of quantitative reduction in their diets. In one group of 12 subjects (Squad A), the diet was reduced so that a loss of 10% in weight was effected in a period of 6 to 8 weeks; this necessitated reduction of the daily caloric intake to 1,900 calories from a previous level of about 4,000 calories. The reduced weight was maintained for a period of 2 months. In a second group of 12 subjects (Squad B), the daily caloric intake was reduced to 1,400 calories for a period of 3 weeks, during which time an average weight loss of 6.5% was effected. With a full diet the subjects gained to the previous weight or above within 5 weeks. During the period of weight loss, there was no evidence of any specific deficiency syndrome; in Squad A there was a continuous negative nitrogen balance during the period of reduced diet. Most of the subjects noted a sensation of cold and marked reduction in perspiration during the period of undernutrition. In Squad B there was some reduction in the rectal temperature. In both groups the average basal pulse rate decreased from 56 to 40, with several individual instances when pulse rates of from 29 to 35 per minute were recorded during the periods of undernutrition. Electrocardiographs showed no abnormalities except sinus bradycardia. Both systolic and diastolic blood pressure were decreased, the average levels of Squad B being reduced from 120/83 to 94/64 after 3 weeks of reduced diet. Striking changes were observed in the basal heat production; in Squad A, at the end of the period of undernutrition the heat per square meter of body surface was 22.1% below the predicted values for individuals of the same height, weight, age and sex. In Squad B there was a 25% reduction in basal metabolism during the 3-week period on reduced caloric intake. With the prolonged reduced diet, there was a marked decrease in sexual interest and expression, which in some subjects reached the point of obliteration. Sexual desires were much less prominent, there was no attraction to the opposite sex and nocturnal emissions and erections were less frequent. There was a distinct return to normal sex interest with resumption of an uncontrolled diet. Several of the subjects developed mild anemia.

Basal metabolism and thyroid. One of the most constant and striking observations in patients with anorexia nervosa is the reduction in basal metabolism. Although all degrees of reduction occur, it is not uncommon to observe basal metabolic rates of below −40%; in *case 1* of the present report, on two occasions the B.M.R. was more than 50% below the predicted level for individuals of the same height, weight, age and sex. Reference has already been made to the striking reduction in heat production which occurred in Benedict's subjects. During recent years advantage has been taken of the reduction in metabolism during undernutrition in the treatment of patients with cardiac disease. Master, Jaffe, and Dack (22) used a restricted diet in the treatment of patients with coronary thrombosis. Decreases in the B.M.R. of from 15 to 30% were shown to have a beneficial effect on the cardiovascular system of these patients. Proger and Magendantz (23) observed beneficial effects in a group of patients with congestive heart failure in whom an average decrease of 18% in the B.M.R. was induced by restriction of the caloric in-

take. The literature contains many other references to reduction in basal metabolism in undernutrition both in man and in the experimental animal.

The cause for the reduction of metabolism and oxygen consumption in undernutrition has been the subject of a good deal of speculation. Benedict (21) suggested that the lowered metabolism was the result of loss of large amounts of nitrogen from the body during periods of undernutrition. Lusk (24) stated, "whether the reduction (in metabolism) is due to a disturbance in the glands of internal secretion, to a diminished secretion of thyroxin in the absence of adequate protein and calories in the diet, for example, is a field for speculation and investigation." Proger and Magendantz (23) suggested that "the general state brought about by prolonged dietary restriction appears to be one of unusual depression of the endocrine glands, possibly through a diminution in the activity of the anterior lobe of the pituitary gland." Master, Jaffe, and Dack (22) felt that the drop in metabolism was a protective adaptation of the body to the low caloric intake but did not believe that it was mediated through the thyroid because in their patients there were no changes in the blood cholesterol or circulation time, or evidence of myxedema. It should be noted, however, that these frequently are not observed in patients with hypothyroidism which occurs as a result of pituitary failure (25).

The literature contains references to morphological changes in the thyroid in inanition both in man (20, 26, 27) and in the experimental animal (26, 28, 29). These changes have consisted of atrophy, flattening of acinar epithelium, increase in colloid, and degenerative changes. Rabinovitch (30) has described the thyroid glands of a small group of guinea pigs fed an inadequate diet resulting in loss of 20 to 30% of their weight in 9 to 11 days. In such animals there was almost complete cessation of proliferative activity; the acinar epithelium was flattened and colloid was hard and dense. These observations have been confirmed and extended by the author (31). The administration of an inadequate diet to guinea pigs, resulting in a loss of from 20 to 30% of body weight in a period of 2 weeks resulted in marked structural changes in the thyroid, characterized by atrophy and flattening of the acinar epithelium and retention of colloid, suggesting a resting, inactive gland (fig. 4). These changes were not affected by the administration of vitamin supplements or by the administration of potassium iodide. Refeeding of such animals resulted in rapid gain in weight and return of thyroid structure to normal (fig. 4). The thyroid of the undernourished guinea pig showed a marked increase in sensitivity to the thyrotropic principle of the anterior hypophysis. In such animals, histological changes indicated that the thyroid could be stimulated by the injection of as little as one-tenth the minimal effective dose for normal animals. The structural changes which occurred in the undernourished animals were identical with those which have been observed in the hypophysectomized animal. The increased sensitivity to stimulation by thyrotropic hormone and the lack of response to potassium iodide are likewise observed in animals in which the pituitary has been removed. These observations were interpreted as indirect evidence suggesting that the atrophic changes in the thyroid in inanition were due to decreased secretion of the anterior pituitary thyrotropic principle. The experimental evidence indicates that the decreased metabolism in undernutrition is associated with changes occurring in the thyroid, and there is reason to believe that these changes are due, in part at least, to diminished pituitary function.

Gonads. Amenorrhea has been present in almost all cases of anorexia nervosa occurring in women, and occasionally has appeared to precede the weight loss. In those cases in which examination of the pelvic organs has been mentioned, small genitalia have almost invariably been found. Examination of the vaginal smears in Richardson's cases showed changes typical of estrogenic deficiency (8). The vaginal smears returned to normal after gain in weight had been effected. In the three men reported in this communication, atrophy of the prostate was marked in each instance and was accompanied by loss of sexual function. The prostatic atrophy was similar in degree to that which occurs in hypopituitarism and castration, in which this finding is the earliest and most common sign of gonadal insufficiency (25, 32, 33).

The deleterious effect of undernutrition on the reproductive organs in man has been amply demonstrated. It will be recalled that Benedict's undernourished subjects noted loss of sexual desire and potency. Amenorrhea and sterility have been observed repeatedly in women during famines (26, 29, 34, 35). Stefko (36) examined the ovaries in 120 cases of starvation and was unable to find a single ovum. In a study of the effect of earlier malnutrition in a group of 148 girls, aged 14 to 18, 28% were found to have hypoplasia of the sex organs, 82 had infantile internal genitalia and in 22% there was marked retardation of puberty. In a group of 700 undernourished boys, aged 7 to 16 years, 27% were found with cryptorchidism, 36.7% with genital infantilism. Fifty per cent of adult starved men had no spermatozoa in the tubules of the testes.

In 1921, Leo Loeb (37) studied the effect of chronic undernutrition in guinea pigs. A reduction in weight of 20 to 30% resulted in atrophic changes in the ovaries. No mature follicles developed and the hypoplastic state of the ovary was considered incompatible with ovulation and the normal sexual cycle. Marrian

and Parkes (38) also reported that partial inanition in rats resulted in ovarian atrophy and anestrus. They observed that the ovaries remained sensitive to stimulation by anterior pituitary extracts and that refeeding resulted in a return of estrus when body weight was regained. Permanent sterility did not result in these animals if full recovery was allowed. Moore and Samuels (39) have described the effects of partial inanition in male animals. Undernourished rats showed changes in the prostate and seminal vesicles similar to those found in the castrate animal. These changes were promptly corrected not only by the testis hormone but also by the administration of the anterior pituitary-like principle obtained from pregnancy urine, suggesting that suppression of the hypophyseal gonadotropic principle was responsible for the deficiency of testis hormone. Breneman (40) attributes decreased testicular weight of chicks on a limited diet to decreased production of pituitary gonadotropic hormones. Selye and Collip (41) also have observed ovarian atrophy in undernourished animals and concluded that under conditions of malnutrition the pituitary secretes less of the gonadotropic principle. Similarly Kurzrok and his associates (42) have attributed the anestrus of undernourished rats to diminished production of the hypophyseal gonadotropic hormone. Mulinos and Pomerantz (43) recently have described the histological changes which occur in the gonads of undernourished rats and have emphasized the similarity of these changes to those which occur after hypophysectomy. The atrophic ovaries of rats killed during chronic inanition showed thecal cells with wheel-like nuclear formations; these cells were indistinguishable from the 'wheel cells' which have been described by Selye, Collip and Thompson (44) as being a typical deficiency reaction of the ovary after hypophysectomy. Similar observations have been described by Stephens and Allen (45) (fig. 4), who also have pointed out the similarity of the histological changes in the ovaries of undernourished guinea pigs to those occurring after hypophysectomy, and have confirmed the responsiveness of the ovaries of the undernourished animals to pituitary extracts containing the gonadotropic principle.

There is a considerable body of clinical and experimental evidence which indicates that the changes in sexual organs and functions which occur in undernutrition are due to atrophic changes of the gonads associated with supression of anterior pituitary gonadotropic function.[2]

Adrenal. There is little clinical evidence of disturbance of adrenal function in patients with anorexia nervosa. Leede (11) attributed many of the changes observed in anorexia nervosa to adrenal insufficiency. In the three patients described in this report low initial serum chloride levels were observed, but may have been due to previous restrictions in sodium chloride intake, rather than to any specific disturbance of the adrenal cortex. The hypotension, and the abnormality in carbohydrate metabolism are similar to those observed in patients with Addison's disease, but may be adequately explained without reference to adrenocortical function. Davis (46) and Stephens (47) have reported normal electrolyte responses to sodium chloride restriction in patients with anorexia nervosa.

Atrophic and degenerative changes in the adrenal glands have been described in experimental and human inanition (20, 26, 29, 36, 48); these changes, however, have been inconstant and have varied with the degree and duration of dietary restriction. In some instances enlargement of the adrenals has been observed after short periods of malnutrition. Recently Mulinos and Pomerantz (42) have described the changes in the adrenal gland in chronic undernutrition in rats. Atrophy of the adrenal cortex was observed, with cellular changes characterized by marked diminution in cytoplasm, nuclear arrangement of chromatin in spoke-like fashion and pigmentary deposits in the zona reticularis. 'Wheel cells' similar to those described in the ovary and testis were observed in the adrenocortical layers. The similarity of these changes to those occurring in the adrenals of hypophysectomized rats was emphasized.

Carbohydrate metabolism. The question of carbohydrate metabolism in anorexia nervosa presents a complex problem. In each of the three patients described in this report a low, flat type of glucose tolerance curve was found and in one patient (*case 1*) increased sensitivity to insulin was demonstrated. In the majority of patients described in the literature, flat glucose tolerance curves have been recorded; in others, however, normal or 'diabetic' types of curves have been found. A clue to the explanation of the variability in types of sugar tolerance curves may be found in the recent review by Chambers dealing with the effect of undernutrition on carbohydrate metabolism (49). In complete inanition (starvation), the administration of glucose may be followed by hyperglycemia and glycosuria (so-called hunger diabetes). It has been shown that this type of reaction is at least partially due to the fact that the tissues of the starved animal lose the ability to burn carbohydrate, as evidenced by the failure of the R.Q. to rise after the administration of a single dose of sugar. With subsequent doses of glucose, the ability to metabolize carbohydrate is slowly regained. It appears that in com-

[2] In a recent publication, McCullagh and Tupper (*Ann. Int. Med.* 14: 817. 1940) reported that qualitative assay showed excessive amounts of urinary gonadotropin in 7 of 18 patients with anorexia nervosa. This finding is interpreted as evidence against pituitary insufficiency as a cause of symptoms in anorexia nervosa.

plete starvation, storage by the glycogen-depleted liver and tissues is unable to cope with the amounts of glucose absorbed from the intestinal tract in the absence of glucose combustion, so that hyperglycemia and glycosuria result. In partial or incomplete inanition, however, the ability of the tissues to burn glucose is retained; under such circumstances, glucose absorbed from the gastrointestinal tract may be quickly removed from the blood stream by the glucose-hungry tissues and the glycogen-depleted liver, so that hyperglycemia does not occur.

Johnson, Sheldon and Newburgh (50) have recently studied the oxidation of carbohydrate by normal human subjects following various degrees of depletion of carbohydrate reserves. When stores were greatly reduced by lowered intake of calories and carbohydrate, impairment of oxidation occurred and considerable portions of the ingested sugar were stored. They concluded that, under such conditions, it appeared more important to replenish the depleted carbohydrate stores than to use the incoming carbohydrate for fuel. Variations in the rate of absorption of ingested glucose will also result in variation in the shape of oral tolerance curves. Cori (51) has shown that in rats starvation decreases the rate of absorption of glucose. The decreased metabolism of experimental hypothyroidism (and presumably that of inanition) also has been shown to be accompanied by a decreased rate of absorption of glucose from the intestine (52). In one of the patients described in this report, a significant increase in R.Q. was observed after the administration of glucose, indicating that sugar was being absorbed and burned, although there was no increase in the blood sugar level. The intravenous sugar tolerance curve in *F. M.* (*case 1*) and in one patient reported by Sheldon and Young (13) indicated that sugar was being removed from the blood stream more rapidly than normal.

Ross (53) and Sheldon and Young (13) have attributed the abnormalities in sugar tolerance in anorexia nervosa to the effect of the previous diet, and feel that it is unnecessary to resort to abnormalities in the endocrine system to explain them. During recent years, Himsworth (54), Conn (55) and others (49) have convincingly demonstrated the effect of the previous diet on the conformation of the glucose tolerance curve. A few days of a diet low in carbohydrate may result in a diabetic type of glucose tolerance curve and decreased sensitivity to insulin in normal or abnormal subjects. A diet high in carbohydrate, however, results in increased glucose tolerance and increased sensitivity to insulin. It appears that these changes are due to the relative carbohydrate content of the diet and may occur independently of the total caloric intake. The factors responsible for these variations in carbohydrate metabolism as a result of dietary changes have not been elucidated but Himsworth (54) suggests that they may be associated with changes in anterior pituitary function.

The conformation of the glucose tolerance curve is the result of a complex combination of factors concerned in carbohydrate metabolism, including the rate of intestinal absorption, removal of glucose from the blood stream for oxidation and storage by the tissues, glycogenesis and glycogenolysis in the liver, and the state of pancreatic, adrenal and pituitary function. The influence of undernutrition on many of these factors is imperfectly understood but may vary with the degree and type of inanition, as indicated above. Until further clinical and experimental information is available, it seems impossible to reduce the effect of undernutrition on carbohydrate metabolism to any simple formula. However, it may be of some significance that the type of glucose tolerance curve most commonly encountered in anorexia nervosa is similar to that most often seen in hypopituitarism.

Pituitary. The similarity of the clinical picture of anorexia nervosa to that of hypophyseal cachexia has been emphasized repeatedly. It has been shown above that the changes which take place in metabolism and thyroid, in sexual function and gonads, in the adrenals, and possibly in carbohydrate metabolism during undernutrition are of the type associated with impairment of anterior pituitary function. There is more direct experimental evidence of pituitary insufficiency in inanition. Jackson (56) studied the effect of inanition and refeeding on the hypophysis of the rat. During undernutrition areas were found in the pars anterior showing marked atrophic and degenerative changes, with cytoplasm vacuolated and reduced in volume. The cells became sparsely granular and tended to lose their specific staining reactions, so that strongly chromophilic cells became weakly chromophilic or even chromophobic. It is of interest that the most striking changes occurred in the granular cells which are presumably responsible for the hormonal activity of the anterior pituitary. Similar structural changes have been observed in the anterior hypophysis in human undernutrition (15, 20, 36). Recently Werner (57) and Mulinos and Pomerantz (39), working with undernourished rats, have confirmed the histological changes described by Jackson. Mason and Wolfe (58), using a transplantation technic, reported that the hypophyses of animals fed an inadequate diet were lower in sex stimulating capacity than those from normal animals. Werner (57) observed that the atrophic ovaries in inanition were similar to those of the hypophysectomized animal and found that they were still normally responsive to gonadotropic substance. He confirmed Mason and Wolfe's observation that the gonadotropic function of the hypophysis was

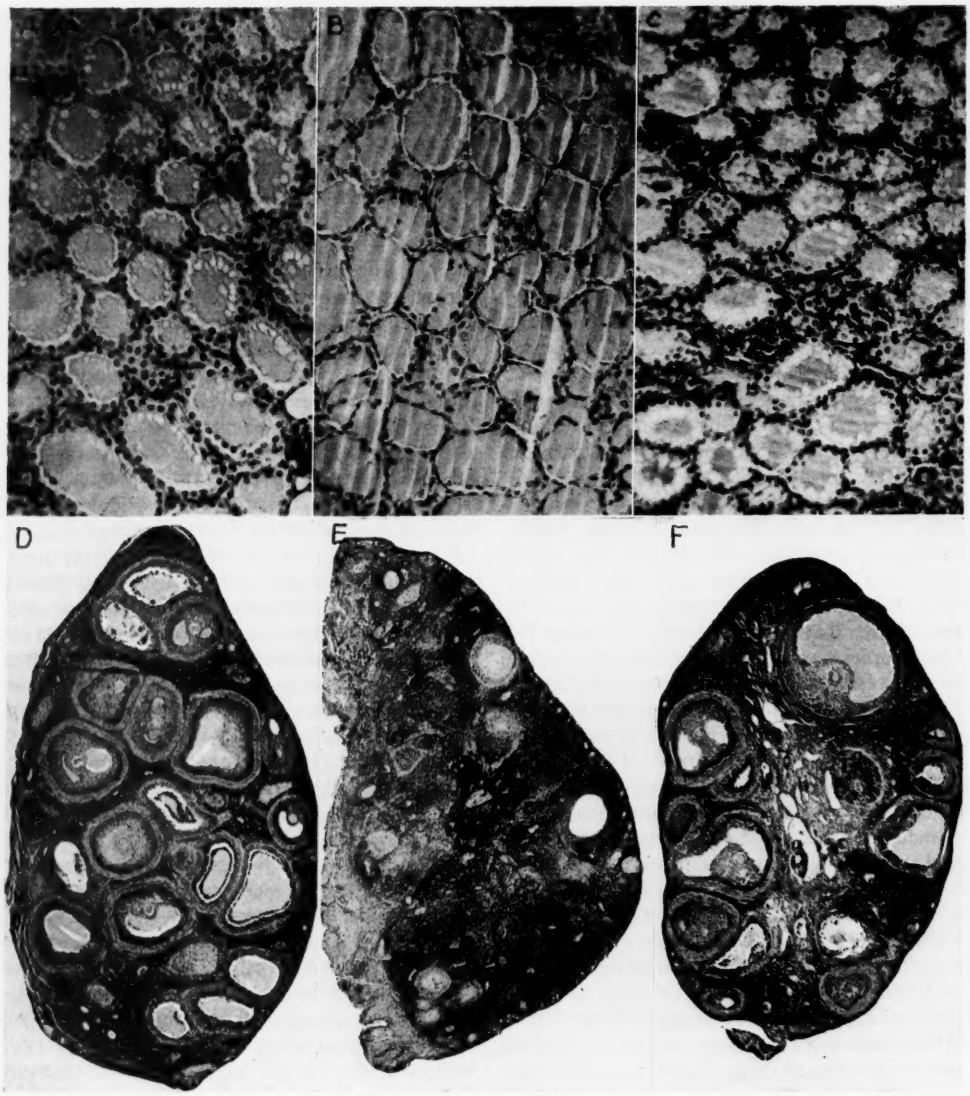

Fig. 4. EFFECT OF UNDERNUTRITION AND REFEEDING ON THE THYROID GLAND (magnification, 200 diameters) AND THE OVARY (magnification, 25 diameters) OF THE GUINEA PIG. A. Upper left, thyroid, normal guinea pig. B. Upper center, thyroid, undernourished guinea pig. C. Upper right, thyroid, undernourished, refed guinea pig. D. Lower left, ovary, normal guinea pig. E. Lower center, ovary, undernourished guinea pig. F. Lower right, ovary, undernourished, refed guinea pig.

decreased in the undernourished animals and also showed that there was failure of the pituitary response to castration; the histological changes and the increase in gonadotropic titer observed in normal animals after removal of the gonads, failed to occur in the undernourished animals.

Reference has already been made to the report of Mulinos and Pomerantz (43) who emphasize the similarity of the histological changes in the organs of undernourished animals to those occurring after hypophysectomy. Their experiments, as well as those of others (31, 41, 45), indicate that at least two factors contribute to the changes observed in the endocrine glands in states of undernutrition. First, there are those changes which result directly from malnutrition due to limitation of calories, vitamins, etc. In addition, a secondary effect, due to the depressing action of inanition on anterior pituitary structure and func-

tion, occurs in those organs (thyroid, gonads, adrenal, etc.) which are dependent on hypophyseal support for maintenance of their normal histology and physiological effects. They regard the state of chronic undernutrition as one of "pseudohypophysectomy."

The changes in the hypophysis which result from underfeeding are apparently reversible. Jackson (56) observed that after 4 weeks of refeeding, the greater part of the anterior hypophysis had returned to normal, although some evidence of atrophy seemed to persist for indefinite periods. In the guinea pigs studied by the author (31), the structural changes in the thyroids of undernourished animals attributed to anterior hypophyseal failure disappeared and the histological picture returned to normal after a period of two weeks refeeding. A similar return toward normalcy was observed in the ovaries of these animals (fig. 4).

In many ways the changes which occur in hibernating animals are similar to those which occur in undernutrition. In 1915 Cushing and Goetsch (59) noted that the physiological phenomena of the hibernating state (subnormal temperature, slow pulse, decreased metabolism, hypoplasia of the sex organs, etc.) bore a marked resemblance to those of clinical hypopituitarism and experimentally induced hypophyseal insufficiency. They observed that in hibernation the pituitary diminished in size and the cells of the pars anterior lost their characteristic staining reaction to acid and basic dyes. At the end of the dormant period, the gland swelled and as the cells enlarged, they again acquired their differential affinity for acid, basic and neutral stains. They expressed the opinion that the hypophysis becomes functionally inactive during the hibernating state. Jackson (56) expressed the opinion that the changes described in the hypophysis during hibernation were probably inanition effects. More recent studies (60) also lead to the conclusion that inactivity of the anterior hypophysis is the primary factor responsible for the phenomena of hibernation.

Recent observations, in particular those of Selye (61), indicate that the anterior pituitary reacts to various types of adverse influences with variations in its functional activity. The hypophyseal response to inanition appears to be of the same nature as that which occurs in hibernation, in the 'alarm reactions' (62), in the variations of thyrotropic and thyroid activity to changes in environmental temperature (63), etc.

There is, then, a considerable body of experimental and clinical evidence both direct and indirect, that many of the clinical manifestations of anorexia nervosa and other types of chronic inanition are due to the effects of undernutrition on the anterior hypophysis, resulting in a diminished secretion of its hormones. Such a view is compatible with the difficulty in distinguishing clinically between anorexia nervosa and Simmonds' disease. The changes which occur in undernutrition may be regarded as expressions of a protective mechanism to compensate for the reduced caloric intake, mediated principally through a functional limitation of pituitary activity, with secondary hypofunction of those glands depending on the hypophysis for maintenance of normal structure and function.

This conception of anorexia nervosa carries with it certain therapeutic implications. In addition to the fundamental principle of psychotherapy directed at the underlying mental disturbance, the sine qua non of treatment should be the administration of a full diet, adequate in all respects, but with particular attention to high caloric value. It has been shown that the changes in endocrine glands occurring in experimental undernutrition may be corrected by refeeding (31, 38, 45, 56). The physiologic disturbances in Benedict's undernourished men disappeared when a full diet was resumed. Complete, although sometimes temporary, cure has been observed repeatedly in patients with anorexia nervosa when the caloric intake has been sufficiently increased, without other therapy. There is reason to believe that attempts to stimulate pituitary and other endocrine functions may be detrimental unless simultaneous attempts to increase the caloric intake are successful. The experimental evidence indicates that the undernourished animal remains fully responsive to the stimulating effects of anterior pituitary extracts (31, 38, 39, 41, 45). However, there is no clear evidence of either favorable or unfavorable effects of anterior pituitary therapy in patients with anorexia nervosa, perhaps because of the relatively low potency of extracts which have been used. The administration of thyroid substance has appeared to have undesirable effects in some patients (6, 8); in others, it has seemed to stimulate the appetite and result in voluntary increase in food intake (4, 12, 64). If the depression of the various endocrine functions in undernutrition may be regarded as a protective mechanism for the conservation of vital processes, then artificial attempts to stimulate endocrine activity would appear to be undesirable.

SUMMARY

Three male patients with anorexia nervosa are described, with particular reference to endocrine studies. The similarity of the clinical picture to that of hypophyseal cachexia is emphasized. In each instance, striking improvement was observed when the caloric intake was increased.

The clinical and experimental literature dealing with the effects of undernutrition on the endocrine glands is reviewed. The evidence indicates that

chronic undernutrition is accompanied by structural and functional alterations in the hypophysis which result in decreased pituitary activity. Alterations in structure and function of the thyroid, gonads and adrenals have been described which are similar to those which occur after hypophysectomy. It is suggested that many of the changes which occur in undernutrition (and in anorexia nervosa) may be regarded as expressions of a protective mechanism to compensate for the reduced caloric intake, mediated principally through a reversible, functional limitation of pituitary activity.

The following concept of the pathogenesis of the clinical picture of anorexia nervosa has been suggested. As a result of a neurosis or other mental abnormality, appetite is lost and voluntary reduction in food intake occurs. Because of the reduced caloric intake, direct effects of undernutrition occur, resulting in atrophic and functional disturbances in the endocrine and other organs. The resulting reduction in pituitary activity is followed by secondary changes in thyroid, gonads, adrenals and possibly in carbohydrate metabolism. These secondary effects of pituitary insufficiency may dominate the clinical picture in anorexia nervosa. These changes, at least to a large extent, are reversible and may be corrected by refeeding. The therapeutic use of endocrine preparations is usually unnecessary and, on theoretical considerations, may be contraindicated.

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A CASE REPORT

ANOREXIA NERVOSA

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MOST CASES heretofore described as anorexia nervosa (functional pituitary cachexia, endogenous emaciation in young women, Simmonds' disease) have shown relatively consistent clinical pictures with only minor variations in the symptomatology during the course of the disease. Little attention has been paid to personality changes that are dependent upon the emotional motivation, yet startling changes in the symptoms may occur so that a diagnosis of anorexia nervosa would not be made during certain phases of the illness. For example, we have seen 4 cases in which there occurred a pathologically increased food intake during one phase of the patient's illness; the presence of such bulimia does not rule out the operation of a psychoneurosis which manifests itself in various ways including anorexia nervosa. Osgood observed bulimia in his published case in which he able to examine the patient at autopsy. We are able to report here a case showing several different clinical pictures in the course of a personality determined disease.

Miss F. R., a 28-year-old white unemployed female stenographer, was admitted to the psychopathic hospital on 5-10-39 upon complaint of her mother and sister because the patient had been unmanageable due to her surreptitious chronic alcoholism, had recently been drinking wood alcohol, and had struck her mother during violent recurrent quarrels. Additional information was given by the sister, a school teacher, who is a well-educated, intelligent, cooperative person, apparently deeply interested in the welfare of the patient.

The present illness apparently began during August, 1935, when the patient began to diet because she had been told in a joking manner by men in her office that she was getting heavy, although she only weighed 112 lb. She gave as an additional rationalization for her dieting that she thought she ought to weigh less than her sister, who was two years older. It was also at this same time that she had been promoted to the position of a private secrtary to a very exacting, insecure man who made unusual demands upon the work abilities of his secretaries, three of whom were said to have left his employ due to "nervous breakdowns." Her promotion was a replacement of her more competent sister who had left this excellent job in order to teach school, since she wanted to make teaching rather than business her career. The resignation of the sister deprived the patient of invaluable support for she had really made possible the advancement of the patient. Another source of emotional stress at this time was her preoccupation over an affair. She had been entertained socially by a prosperous 38-year-old married man who took her to expensive restaurants and night clubs but to whom her family objected strenuously because of his previous marriage, his age and his religion. In August, 1935, the patient finally capitulated to her family's wishes by giving up her married friend, even after she had been told by his wife that she might marry the man after the divorce. In November the man married suddenly, without telling the patient. This was a severe blow to her although there was no logical reason for him to tell her of his intentions since she had definitely renounced her interest in him. At this time she experienced her first "convulsion," a stiffening of the arms and feet lasting only a few moments without the loss of consciousness; placing the hands in cold water seemed to give relief. These continued at occasional intervals until 1938.

The conscious dieting started in August, continued until December, 1935, when her weight dropped to 92 lb. In spite of her apparent desire to eat, from this time on she seemed unable to do so. When her weight reached the alarming figure of 72 lb. in May, 1936, the family forced her into a hospital where she stayed for 4 weeks with a 13 lb. gain in weight. She was given insulin to stimulate her appetite but went into coma on three occasions. She now returned to her job without any further loss of time from work until her discharge "for her own good" in July, 1937, when she weighed 58 lb. Her employers had no complaint about her work but did not want to take the responsibility for her health. She had worked very hard, coming in early, staying late, assuming much responsibiilty. Her competence was unquestioned and her energy remarkable, for she was hyperactive even at the time of her discharge when the emaciation was extreme. Amenorrhea began about May, 1937, when the starvation became pronounced and continued until her "recovery" during hospitalization in March, 1939.

The patient now spent her time at home with her partially invalided father in a small flat. Efforts to increase her food intake were unsuccessful. In August, 1937, it was observed that her hair was falling out and that she had more "convulsions." These were said to be due to hypoparathyroidism by a physician. The latter prescribed bitters and brandy as a stomachic in December, 1937, after which the family noticed an increased intake of alcohol. She was hospitalized two weeks for the treatment of the alcoholism in January, 1938, without improvement. Gradually she spent more time sleeping in the stupor created by the alcohol, which she obtained by sly or dishonest means

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and imbibed surreptitiously. Her father died in May, 1938; she was obviously drunk at his wake. Due to her unreliability, stubbornness, lying, etc., she was committed as a voluntary patient to Elgin State Hospital from June, 1938, until April, 1939.

The patient improved remarkably at the State Hospital, gaining over 40 lb. She seemed quite happy in her job as waitress and kitchen employee, giving no hint that she had any ambitions in the outside world. It is probable that she derived rather specific satisfaction from working with food and being able to give it to other people. Her prettiness and charm returned so that she became a very popular girl. When her apparent return to normality seemed stable her discharge from the hospital was discussed by the staff physicians. She now began to steal eggs and other produce in a manner which would guarantee her detection, sold these articles for small amounts of money with which she purchased alcohol, in an obvious attempt to provoke the staff physicians into prolonging her hospitalization. She was discharged on April 2, 1939, in spite of her attempts to stay, because she did not seem like a true alcoholic to the staff. They advised that she be allowed to live alone, which she did at a girls' boarding club for several days, meanwhile writing her mother very affectionate letters in a stilted, childish manner. Her alcoholism became so severe that her mother and sister took her to their home against the physicians' advice. Here she stole money, lied shamelessly and on one occasion was publicly incontinent. Her irritability increased, with assault upon her mother in her rages. She made no attempt to rehabilitate herself in any way although she claimed she was trying, in the manner reminiscent of alcoholics or addicts. She was sent back to the State Hospital, which she seemed to welcome, for it seemed to provide both the security and the degradation she required. The contrast between the cultivated efficient secretary in 1935 without any obvious symptoms and the poorly integrated, unstable ward patient of 1938 is sufficiently startling to call attention to the fact that there may be gross changes in the clinical picture of a person with anorexia nervosa. Her menses were now regular, her weight, 112 lb.; there was no anorexia nor any other pertinent abnormal physical finding.

The following excerpts from her developmental history help us understand the illness. The mother did not welcome her first child, nursing her over 16 months in order to prevent another pregnancy. The patient was born two years after her sister. (The history that the mother attempted to prevent the birth of the patient by prolonged nursing of an older child has been found here in another case of 10 years' duration which will be reported by Dr. K. R. Eissler.) The pregnancy was uneventful but the delivery difficult because she was a "heavy, fat" baby. She was also nursed over 16 months to prevent another pregnancy. The mother was partial to the first child from the first because of her deftness, while the father seemed to favor the patient. The patient grew slowly and was sluggish in comparison with her sister, yet learned toilet habits easily within the first 14 months. The mother entertained her while she was at stool. She was never a feeding problem. At the age of two, she had a severe pneumonia, with the usual overindulgence during her long convalescence. After her third year, she showed violent temper tantrums when denied food. During her fifth year she was spanked for lying by her father, which she says she resented, but did not provoke him to do it again. The lie was a fantastic tale about a boy hurting her foot, so that she would not have to admit that she really hurt her foot by her own clumsiness. She was now definitely overly sensitive, overly obedient, overly clean, jealous of her sister, trying hard to win the affection of the too strict mother by being an "angel" child. Her general health and progress were good. In 1917, aged seven, the patient's life was radically altered by the invalidism of her father, to whom she was a nurse for some years, helping him with bed care, bathing and massage. Her mother began working in 1917 and continued to do so until 1931. The patient was, therefore, a kind of "wife" to her father, a function she enjoyed very much. In school, she was spoiled by everyone, including the teachers, because she was a very pretty, docile child who knew how to attract affection. She used her wiles to escape emancipation and responsibilities yet, paradoxically, had practically adult cares in helping her father. Later it appears as if she thought of these adult responsibilities as being too onerous and did not believe that what she gained in affection from her father was sufficient compensation for her hardship. Furthermore, she risked her mother's displeasure because of her close relationship to her father. She became increasingly perfectionistic, an extremist in all she tried to do, worked hard to outdo others rather than to master the subject for its own sake, was intolerant of rivalry and covetous of others, especially her sister. Her mother sent her to dramatic, dancing and singing schools, where she became self-contained, socially polished and increasingly exhibitionistic. In 1927, at the age of 16, her menses began very irregularly without pain, flowing only in small amounts. There was a 9 months' interval between the first and second periods and 2 to 3 months' intervals between succeeding periods. Finishing high school that year, she tried to emulate her sister in passing entrance examinations into Normal School but failed. Her sister, meanwhile, had graduated with honors but since good teaching jobs were scarce had obtained a good job with a large corporation. The patient now went to work in the same corporation due to her sister's influence, working at a desk next to her. The older girl was undoubtedly superior, acting as disciplinarian as well as a guide and helper. The patient's work was excellent, however, and she had no difficulties until she received her promotion.

A survey of the probable course of development of

the illness reveals that this patient was strongly dependent upon a strict mother who rejected her, causing a deep inner insecurity. The patient was able to get the love she craved from her father, but only at the threat of loss of love from the mother. This acceptance of her father is already a secondary defense against the insecurity caused by the rejection by the mother. She tried to gain her mother's affection by passive obedience to her demands. Her dependence reactions increased as she grew older, as clearly seen in her unwillingness to walk until 3 years even though she was able to do so at 18 months. Her habits at stool implied "I am giving up something, so you must give me love and attention." Her means of getting attention by obedience, clean clothes, etc. intensified both her narcissism and her exhibitionism. As she grew up, her perfectionistic, extremist character intensified her immature adjustment. Her compulsive trends are not of the retentive type, but rather of the type exemplified by "I give in order to receive." She was unwilling to accept physical or psychological emancipation avoiding the threat of heterosexuality. This unstable adjustment at 24 was rudely upset by the rather unusual set of precipitating circumstances which found her peculiarly vulnerable since they recapitulate parts of the early history we have reviewed. Suddenly, she is forced into a superior position because her sister does not want it, and she is left without the sister's support. She now gains the boss just as earlier she did the father, but at the cost of losing the sister and also being forced to work excessively since her boss was so exacting. Her guilt is mobilized because she has won him, but the gain is not great enough to make her comfortable. She acquires a lover who treats her to elegant food, which to her is the equivalent of affection, but whom she must renounce because of her mother's prejudice; this arouses resentment and more guilt feelings, and with renunciation both her hostility and her eroticism must be severely repressed. The childhood pattern of dependence on mother and working for father is duplicated with dissatisfaction. The resentment and guilt cause self-destructive tendencies which are expressed in her self-deprivation of food. Secondarily this deprivation may be also conceived as a denial of her growing up and of her sexuality. There is also another gain in that it satisfies her desire to exhibit herself for everyone looked at her when she was very thin.

Three additional attempts at parole from the State Hospital have resulted in failure since the patient returns to her psychotic-like behavior upon each discharge. In the hospital her behavior is entirely reasonable. It seems as if the hospital gives her the security and the punishment required by her emotional organization. From the history we get some clues about the principal motives for her bizarre behavior. The distinct phases in the development of this disease can be followed clearly from the beginning when she was a competent, attractive secretary, through the dieting stage to the typical clinical picture of anorexia nervosa which later developed into a state of chronic alcoholism. In the environment of the State Hospital she "recovered" sufficiently to seem quite normal although her present levels of achievement are much lower than before. She sacrifices the rewards of maturity in order to escape its responsibilities.

SUMMARY

A case of anorexia nervosa with typical findings including marked loss of weight and amenorrhea but retaining restless energy is presented. Special emphasis is given to the motivations which are apparent in causing the illness, and the progress during a 5-year period described. The fact that the patient showed phases of chronic alcoholism with psychotic-like behavior following the phase of anorexia nervosa, with return to "normal" behavior and good physical health upon each return to a State Hospital bespeaks an emotional rather than an organic cause for her illness. This case illustrates the thesis that anorexia nervosa is not a strict clinical entity, either psychiatric or medical, that the clinical picture undergoes wide variations, and that the causes for the illness are specifically determined by the personality of the patient.

ANOREXIA NERVOSA

CASE REPORT WITH AUTOPSY FINDINGS

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THE RELATIVE SCARCITY of case reports with examination of the brain of persons suffering from the condition variously described as anorexia nervosa, pituitary cachexia or endogenous emaciation in young females, prompts us to publish the findings in this case. It resembles others published in the literature, notable that of Osgood (1). The reviews of Silver (2), Richardson (3), and others (4, 5) discuss the clinical and pathological aspects of this condition in detail.

E. A., an unmarried, white, Protestant female stenographer of 27, entered the service of Dr. Louis Leiter at the University of Chicago Clinics on 11/21/33 complaining of weakness, loss of weight and amenorrhea. History given by the patient and the mother states that the patient was perfectly well until 1919. While in the 8th grade at the age of 13 the patient became excessively fatigued and "nervous," ostensibly because of "overwork." She was said to have had a "nervous breakdown" for the following year and one-half though she did not quit school. She was put on sedation and partial rest, which apparently enabled her to go on. About the same time (no really accurate data) as the onset of the fatigue, she began to menstruate. The flow was excessive, accompanied by severe pain, but appeared regularly at 28 to 30-day intervals for a duration of 5 days. The flow continued regularly until April, 1925. During the period of improvement of her "nervousness" in 1920 she began to have abdominal pain which was increased during the menses, and constipation was coincident with the pain. Weight at this time was 117 lb. During 1924, she experienced occasional headaches with nausea and vomiting. These became more pronounced when the menses stopped in April, 1925. The vomiting then became more severe, coming on usually after a large meal which seemed to cause a distressing sensation of fullness in the upper abdomen. Nausea was not present at that time. No blood was present in the emesis until shortly before the operation in October, 1925, when she vomited for 3 hours and produced a small amount of bright red blood. Peptic ulcer was suspected, but none was found on operation; her appendix was removed and adhesions about the gall bladder freed. She weighed 108 lb. before operation but continued to lose weight on a Sippy regime. In 1926, she weighed 65 lb. During 1927, she had headaches without any nausea or vomiting; later they gradually became less frequent.

In January, 1928, ankle edema was noticed, and in May of that year she entered the Presbyterian Hospital complaining of weakness, emaciation, weight loss, headache, amenorrhea, ankle edema, constipation and bloody stools. Up to this time she had been working steadily after finishing high school, where she had an excellent scholastic and social record. She had become engaged to a competent, personable boy in 1925, but broke the engagement at the time of her hospitalization, in May–June, 1928. Then she was found to weigh 79 lb. with no pertinent pathological physical findings. (No note made of ankle edema.)

Laboratory findings were: B.P. 92/67; Hb 66%; R.B.C. 3.93; W.B.C. 7,650. Ewald test showed no free acidity and total acidity of 34; free acid was found in some of the emesis. Basal metabolic rate on June 1, 1928, was −51% and −52%; June 4, −16%, June 6, −23%; June 26, −5%. Blood chemistry on June 4: blood calcium, 10.5 mg.; carbon dioxide, 49.4 vol.%; sugar, 81.6; chlorides, 460; urea, 13.8; and N.P.N., 34.3. Results of x-rays of the chest, barium meal and enema, skull, lumbar spine and pelvis were all negative. Discharged July 11, 1928, weighing 76.0 lb.

Her second admission, Nov. 7, 1928, revealed no new findings except a generalized edema including the legs, trunk and face. She had gained 10 lb. very rapidly during the time the edema increased. Thyroid gland, 3 to 8 grains daily, brought her B.M.R. up to +4% on Nov. 1, 1928, but did not improve her condition. Parathormone, 2 cc. was given intramuscularly every morning for 7 days without benefit. Calcium lactate, 30 grains, started Nov. 19. Laboratory findings on 11/23/28: P.S.P. 66%; urine and stools, negative; N.P.N. 27.8; carbon dioxide 68.3 vol.%; glucose 85 mg.%; chlorides 506. Discharged Nov. 27, 1928, weighing 78.8 lb.

During March, 1929, the patient was seen at the Mayo Clinic. At this time, she weighed 85 lb.; B.P. was 105/60; the pulse and temperature were normal. There was edema of the feet, ankles, legs, thighs and buttocks. Urine test results were negative. Blood H.G.B. was 71%; R.B.C., 4.2; W.B.C., 3,600; P 66; L 29; M 3%; Tr. 2%; Wassermann test result, negative. Gastric analysis showed a hypochlorhydria with no free acid, no food remnants, nor blood in the contents. Total acidity varied from 16 to 24; two teeth had periapical abscesses. X-ray results of the stomach, colon, chest, right knee, lumbar spine and sacroiliacs were all negative. The B.M.R.'s were −9, −20,

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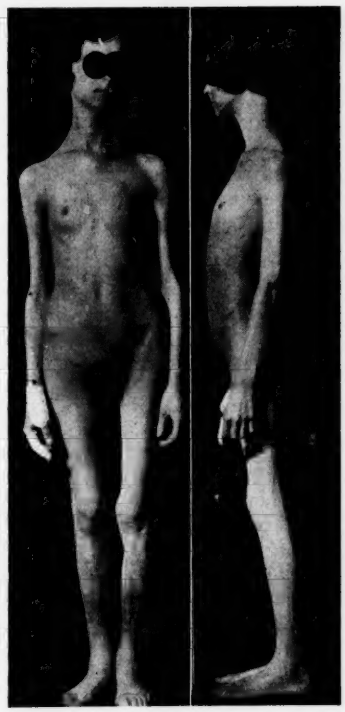

PATIENT, AGE 27, NOVEMBER, 1933.

−22. Blood calcium was 10.5 mg.%. "It seemed to be the consensus of opinion that her condition was due to a malnutrition in association with an anorexia nervosa complex."

The third admission to the Presbyterian Hospital on Nov. 19, 1929, revealed no new complaints. Weight was 73 lb.; B.P., 120/75; H.G.B. 70%; R.B.C. 4.04; W.B.C. 5,000; differential count P 57; L 40; M 0; E 0; B 0; B.M.R., −21. Blood chemistry: urea N 7.06; (food intake poor; amount of protein ingestion not known); uric acid 3.4; creatinine 1.1; N.P.N. 21.6; CO_2 78.8; sugar 79; chlorides 470; calcium 9.7. The B.M.R. on Dec. 6, 1929, was −15. Weight was 68 lb. All x-ray results were negative. She was given courses of thyroid gland, liver extract and parathyroid extract without benefit. She was discharged 12/25/29, weighing 69 lb.

The patient worked and rested alternately during the years 1930 to 1933. Visited a tuberculosis sanitarium, where a complete examination, including stereoscopic x-rays of the chest, revealed no pathology. She was quite active during most of this time and continued working after the last hospitalization. Little accurate information about her physical condition during this time is available, until her entrance into the Billings Hospital on Nov. 21, 1933. Her complaints were the same as those described above. Her teeth had all been removed in July, 1933, because they were carious. Weight on entrance was 71 lb.; height 161.5 cm. Temperature varied from 96.4° to 98.2° F. Pulse was 64–100; respirations, 18–20; B.P., 88/54 to 110/55. With loss of edema there was a concomitant loss of weight down to 61 lb. She was amiable, cooperative, and felt quite well. Except for the emaciation, generalized edema and an infantile uterus, there were no positive physical findings. The hair distribution was essentially normal on the head and in the axillae but the pubic hair was sparse. The numerous laboratory tests will be summarized since nothing is gained by citing each result. B.M.R.'s were fairly uniform at about −38 until 12/19/34; after this showed values of −11, −13, −15. Histamine tests showed free acid. X-rays showed no pathology except a generalized osteoporosis. Specific dynamic action of proteins was normal. Urinary nitrogen excretion was very low (2–3 gm.) indicating a rapid storage of nitrogen although it was some time before the staff was sure she was actually retaining the diet measured out for her, for she often surreptitiously vomited food after meals. The plasma proteins were very low, 4.88 and 5.16 gm.% (N = 6–8). Albumin-globulin ratios were 1.82/3.07 = 0.59, 2.47/2.69 = 0.91; N.P.N. 15 and 21 mg.% (N = 25–35); (protein intake not known); glucose, 51.0 mg.%; cholesterol, 240. Stools were negative. Urine was usually negative, but at times showed traces of albumin, sugar, diacetic acid and acetone; no R.B.C. or casts; W.B.C. 4,800; H.G.B. 83 (Sahli); R.B.C. 4.32. The x-ray results of the skull, chest and bones were negative except for the suggestion of generalized osteoporosis. The heart was 17% undersize from the film tracing and the E.K.G. showed a sinus bradycardia. During the last week in December, 1933, a dusky cyanosis of the legs became apparent, which at times became a frank bright hyperemia. On 12/27/33, the N.P.N., 30; cholesterol, 197; plasma proteins, 5.42 gm.% (N = 6–8), A/G = 2/58/2.84 = .91.

The patient's general condition improved gradually in the hospital although occasional headaches, abdominal discomfort, vomiting, edema and cyanosis of legs continued. It was noticed that the patient was unreliable in reporting her food intake, so that the quantitative studies of urine and stools attempted were not accurate. The head aches were relieved by aspirin and the abdominal distress by massage. Tr. belladonna and allonal were also given for symptomatic relief. The weight gain was very slow, even when her intake seemed to be consistently over 3,000 calories per day. On 3/6/34 the N.P.N. was 19; plasma protein 6.48; A/G 3.27/3.21 = 1.02; TN 1,056; B.M.R. −19. Complete ophthalmological examination of vision, retinae, fields, etc., revealed no abnormal findings. She was discharged on 3/20/34 weighing 75.5 lb.

There was general agreement from the previous history and clinical findings that a diagnosis of primary anterior pituitary deficiency or Simmonds' disease was unwarranted, and that the entire picture could be explained on the basis of severe undernutrition secondary to a marked emotional disturbance. The edema was typical of that seen in nutritional disorders, complicated by the disturbed superficial venous circulation in the legs. There was no evidence of pellagra or other gross vitamin deficiencies. The recurrent appearance of the edema seemed to be related to

the nutritional and mechanical factors in a patient with low plasma proteins. The low urinary nitrogen, low basal metabolic rate, low urinary creatinine and presence of creatine seemed best explainable as secondary to the loss of weight and muscle tissue. The amenorrhea could also be secondary to the malnutrition. Unfortunately, the actual caloric intake was uncertain since the patient vomited some of the measured diet on some days and surreptitiously ate additional food from her roommate's tray on others, in spite of being carefully watched. In four weeks, striking changes occurred, in that the B.M.R. rose from −38 to −19; plasma albumin rose from 1.82 to 2.47; loss of 10.1 lb. in 8 days due to loss of edema was followed by a gain of 9.2 lb., a part of which was edema. There was no diarrhea during the period of forced feeding; the nitrogen and fat contents of the stools were not abnormal.

Efforts to elicit the emotional causes of this anorexia revealed that the patient had always been an intelligent, successful, well liked, idealistic, perfectionistic girl who was inclined to have her own way. Her former fiancé characterized her as the most perfect person he ever expected to know, the model to her friends, idolized by many as brilliant, clever, unafraid of new jobs, yet kind and thoughtful of others. She was very attractive in appearance before the onset of the severe phase of her illness. She had complained of stomach aches early in her high school career without being grossly handicapped by them. The same man said that she was so closely attached to her family that he doubted whether they would ever have lived alone. She seemed principally attached to her mother, but was also excessively concerned at times about a ne'er-do-well brother.

Her mother was very proud of her but could not give pertinent information beyond admitting a deep attachment to the patient. There was no significant history of neurotic behavior in infancy and childhood. The patient was breast fed for a year and presented no feeding problem. No history of domestic discord, but this is not reliable data since the interviews were brief and superficial. Dr. Alfred Adler of New York saw her once, called her a "skillful neurotic" without giving another diagnosis. She was seen once by two other psychiatrists who made no diagnosis. In spite of her perfectionistic trends, she did not present the typical picture of an obsessive-compulsive neurosis, although she had some of the characteristics associated with that syndrome.

The patient was not seen again in the hospital though she wrote a pleasant letter expressing her gratitude to the staff and mentioned that her inability to come to the hospital was due to her working steadily. She said that she was reasonably comfortable with only occasional headaches or backaches when overly tired; weight was maintained around 75–80 lb. She was able to work from July, 1934, to March, 1935, walked 24 miles on a holiday and seemed to be in good condition. In March, she became too weak to work, was invalided and died after a short acute illness in June, 1935, with a clinical diagnosis of miliary tuberculosis with tuberculous meningitis.

The autopsy findings of the Presbyterian hospital, made available to us by courtesy of Drs. J. B. Eyerly and Loren W. Avery, follow in part.

Histology. In one section of ovary, 10 by 5 mm., 2 immature follicles are observed. The wall of a cyst is present, the lining composed of a single layer of flattened cuboidal, epithelial cells. In another section of ovary there is a corpus albicans and 2 follicular cysts about as large as a low-power field. In this section also, follicles are sparse.

In a section of spleen there are several miliary tubercles. Caseation is slight. Langhans giant cells are present in each one. Epithelioid cells and lymphocytes are abundant in the tubercles. There are small regions of hemosiderin pigmentation of macrophages. Malpighian corpuscles are small. There are very few erythrocytes in the sinusoids. The predominant cells in the splenic pulp are cells of the stroma and littoral cells, the majority of which are small.

In a section of thyroid gland there is only slight variation in size of the follicles. The majority contain colloid material, and their cells are flattened cuboidal. There are occasional small groups of follicles that are small, and the lining cells hyperplastic. There are no lymphoid infiltrations. There are two small regions where the follicles have disappeared, and there is an increase in fibrous tissue.

In a section of adrenal gland, the cortical cells have the usual vacuolated cytoplasm. At the junstion of cortex and medulla there are no unusual cellular infiltrations. The adrenal gland is of the average size.

In a section of pituitary gland, which has the average dimensions, the architecture is quite normal. The majority of cells are chromophobe. There is no increase of basophilic cells. The eosinophilic chromophil cells have the usual distribution.

In a section of liver, one miliary tubercle is observed. There is a slight increase of lymphocytic cells in the periportal regions, and no changes in the bile ducts. The venous sinusoids are narrow. There are no other unusual changes.

There is no change in the cervix. The endometrial glands are sparse.

In a section of kidney there are occasional regions near the outer surface where a few glomeruli are partially obliterated by hyalinization. The accompanying convoluted tubercules are atrophic or have disappeared. A number of the glomeruli are small, and resemble slightly the appearance of a glomerulus in the infantile kidney. There are other glomeruli in which the normal architecture is altered by adherence of the loops to the capsule and proliferation of cells at these regions of adherence. Usually, the fibrous capsule is also slightly increased in thickness. The alterations in the glomeruli supersede the amount of atrophy of the convoluted tuberules. There is no sclerosis of the arcuate arteries. There are no unusual changes in the afferent

glomerular arteries. There are usually several glomeruli altered together, suggesting arterial distribution. The essential change in these glomeruli is atrophy. The alterations in the arterioles, however, are not adequate to explain the degree of change.

In a section of lung there is an encapsulated, caseous, tuberculous nodule, a few small regions of bronchopneumonia to a minimal extent, and one small region of tuberculous bronchopneumonia.

The most significant chronic change is found in the kidneys, where there is disseminated atrophy of the groups of glomeruli of unexplained origin. Apparently, the immediate cause of death was miliary tuberculosis. There are no significant changes in the adrenal glands, thyroid, pituitary or pancreas. There are follicular cysts of the ovary, and immature follicles are sparse.

It is unfortunate that there are not enough sections to make a complete serial section of the hypophysis with cell counts, but those available show no evidence of abnormality. We can be certain of the absence of all massive lesions (vascular, luetic, tuberculous, atrophic) such as have been described since Simmonds (6) and Falta (7) and most convincingly demonstrated recently in a routine series of autopsies on women dying following pregnancy by Sheehan (8).

COMMENT

This patient showed all of the usual signs that are described in pituitary cachexia, including anorexia, extreme emaciation with loss of teeth and pubic hair, amenorrhea, hypotension, low basal metabolism and low fasting blood sugar. She also had fairly persistent headaches, vomiting, diarrhea without any organic cause apparent to the numerous experienced physicians who examined her. At times bulimia alternated with the anorexia. That the deep-seated abnormal character traits were sufficient to account for her behavior seems likely. She had the characteristic startling hyperactivity common in patients diagnosed as having anorexia nervosa.

This patient was observed by 4 groups of clinicians over a period of 10 years (1925–1935) without evidence of organic disease. The terminal miliary tuberculosis with meningitis was a recent infection which does not account for the illness which began with vomiting and anorexia in the fall of 1924.

SUMMARY

The words of Osgood (1) can be quoted as applicable to our case: "A patient having a complete clinical and laboratory picture of pituitary cachexia with a normal pituitary gland is described. No explanation for this syndrome was discovered either during life or at autopsy." We believe that the evidence we have concerning the personality of the patient justifies the inclusion of this case in the group described by Sir William Gull as anorexia nervosa (9). He believed this condition to be due to a "morbid mental state" and a large majority of current writers agree with him. It is hoped that thorough psychiatric investigations will be carried out in such cases to make possible a more complete correlation of the medical, anatomical and psychological findings.

We wish to thank Drs. J. B. Eyerly, Louis Leiter and W. Z. Palmer for permission to use their material in this case.

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NEWS ITEMS

DR. EDWARD A. DOISY, for the past eighteen years professor of biochemistry at the School of Medicine, Saint Louis University, has been awarded the Willard Gibbs Medal for 1941 by the Chicago Section of the American Chemical Society.

This award is made annually to a scientist "whose work in either pure or applied chemistry has received worldwide recognition."

Dr. Doisy isolated theelin in 1929 and dihydrotheelin in 1936. An investigation of vitamin K directed by him in 1939 led to the isolation from natural sources such as dried alfalfa leaf meal and putrefied sardine meal, of two pure substances possessing vitamin K activity. The structures of both were determined and one was produced synthetically. This work resulted in the recognition of the antihemorrhagic potency of the chemical compounds known as 1,4-naphthoquinones. Some of his earlier studies included the preparation of insulin, the analysis of nervous tissue, creatine and creatinine metabolism, purine metabolism, determination of sodium, potassium, chloride and phosphate in tissues, and carbon dioxide transportation of blood.

DR. ELMER L. SEVRINGHAUS, President of the Association for the Study of Internal Secretions, has received the first of the "government travel grants." These grants provide funds for the exchange of cultural, professional and artistic leaders between the United States and the other American republics. Dr. Sevringhaus left the United States by plane for Argentina and Uruguay late in February. He will give several lectures in Buenos Aires and Montevideo in addition to attending the Pan American Congress of Endocrinology in Montevideo from March 5th to 8th. Dr. Sevringhaus has been asked to go as the official representative from the United States. This appointment was ratified by President Roosevelt. Dr. Sevringhaus will include a report of the meeting of the Congress in his presidential address to the Association for the Study of Internal Secretions at its annual meeting in May at Atlantic City.

THE U. S. PHARMACOPOEIA Endocrine and Hormone Advisory Board held a conference on the Standardization and Assay of Hormones, in New York City on February 15th. Dr. Charles L. Brown, Chairman of the Advisory Board presided.

The Conference discussed the problems involved in setting up standards and assay methods for a number of hormones, with the ultimate aim of including these in the U. S. Pharmacopoeia. Chairmen of Sub-Committees for further studies are as follows:

Estrone and estradiol benzoate—Dr. S. A. Thayer, St. Louis University Medical School.

Progesterone—Dr. Willard M. Allen, Washington University School of Medicine.

Testosterone—Dr. Ralph I. Dorfman, Yale University Medical School.

Chorionic Gonadotropin—Dr. Gregory Pincus, Clark University Medical School.

Adrenal Cortical Extract and Desoxycorticosterone Acetate—Dr. Arthur Grollman, Johns Hopkins University School of Medicine.

Prolactin—Dr. E. T. Engle, Columbia University School of Medicine.

THE AMERICAN ASSOCIATION FOR THE STUDY OF GOITER is again offering the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The essays may cover either clinical or research investigations and should not exceed 3,000 words in length. Further information may be obtained from Dr. W. Blair Mosser, 133 Biddle Street, Kane, Pennsylvania. The award will be made at the annual meeting in Boston, which will be held on May 26, 27 and 28.

APPLICATIONS for financial aid during the fiscal year beginning July 1, in support of work on fundamental problems of sex and reproduction, should be received by the Committee for Research in Problems of Sex, National Research Council, before April 1. The applications should be sent to the chairman, Dr. Robert M. Yerkes, Yale School of Medicine, New Haven, Connecticut. In accordance with current policy, the Committee will give preference to proposals for the investigation of neurological, psycho-biological and behavioral problems; however, hormonal investigations continue to command the interest and support of the committee.

THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY of the University of Chicago and the Chicago Lying-in Hospital through the cooperation of the Children's Bureau, U. S. Department of Labor and the Illinois State Department of Public Health offers five postgraduate courses of four weeks each between January 6 and June 21. The beginning dates of each are: January 6, February 10, March 17, April 21, and May 26. All the members of the department and all services and units of the institution participate in the instruction. Only a limited number of postgraduate students is accepted for each period. A deposit of $25.00 is required, of which $10.00 is returned on completion of the course. All communications should be addressed to: POSTGRADUATE COURSE, 5848 DREXEL AVENUE, CHICAGO, ILLINOIS.

Abstracts of
CURRENT CLINICAL LITERATURE

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ADRENALS

ANDERSON, E., W. HAYMAKER AND E. HENDERSON.

Successful sublingual therapy in Addison's disease. *J.A.M.A.* 115: 2167. 1940.

While desoxycorticosterone is almost valueless when given orally, Anderson and her colleagues have found it is rapidly absorbed if given sublingually dissolved in propylene glycol. They use a solution which contains 1 mg. drop of solution. The patients regulate their dosage according to need and are as effectively relieved as by parenteral administration.—C. P.

ANONYMOUS.

Treatment of Addison's disease. *Lancet* 239: 200. 1940.

Treatment of severe Addison's disease with adrenal cortical extracts is very costly (up to $2,000 yearly). Synthetic desoxycorticosterone is much less expensive and has now been used successfully for 2 yr. Implantation of pellets obviates the necessity for frequent injs. At the crisis all cases must receive cortical extract alone or the extract plus desoxycorticosterone, salt and glucose. Mild cases can be kept in good health by simply taking up to 20 g. of extra NaCl daily and moderate cases maintained by pellet implantation or inj. of the synthetic drug and added salt.—J. B. Paton.

BONDURANT, C. P., AND C. CAMPBELL.

Adrenal cortex extract in the treatment of bromide eruption and bromide intoxication. *J.A.M.A.* 116: 100. 1941.

Adrenal cortex extract (eschatin) was used in treating 9 cases of severe bromide intoxication and 7 cases of induced bromism in epileptics. Five cc. of eschatin was given daily, and the dietary NaCl was augmented by 6 to 10 m. daily. Two cases with psychosis required 15 days to recover on NaCl alone, while 7 cases on cortical extract and NaCl recovered in an average of 5 to 6 days. Skin trauma was found to be a factor in the etiology of the bromide skin rash.—C. P.

DANCIGER, J. A.

Fulminating meningococcemia with bilateral adrenal hemorrhage (Waterhouse-Friderichsen Syndrome). *J. Pediat.* 16: 495. 1940.

Seventy-five cases of this disease have been described in the literature: 70% were under 2 years of age and 95% under 6. The meningococcus was found in the blood stream in 70% of the cases. Symptomatology consists of sudden onset, restlessness, vomiting, diarrhea, cyanois, purpura, high fever, coma and death. All of the cases terminated fatally, the majority within 24 hours. Both adrenals showed hemorrhages in most of the autopsies involving both cortex and medulla. The condition must be differentiated from adrenal hemorrhage of the new born, and traumatic adrenal hemorrhage. A case is reported in a 3-year-old boy with autopsy findings.—M. B. G.

DURANTE, L.

Extirpation of the adrenal medulla in the hypertensive polycythemia of Geisboeck. *Ormoni, Turin* 2: 31. 1940.

The clinical picture of the hypertensive polycythemia of Geisboeck is discussed in detail, and differential diagnosis from the polycythemia rubra of Vaquez is tabulated. Hess believes symptoms of hypertensive polycythemia are a defense mechanism against hyperactivity of the adrenal medulla. Extirpation of medullary substance in a 56-year-old woman with hypertensive polycythemia produced results confirming Hess' theory.—G. A. E.

HOLMES, E., AND H. LEHMANN.

On the relationship of lesions of the suprarenal gland to diphtheritic toxemia. *Brit. J. Exper. Pathol.* p. 196. 1940.

Diphtheritic toxemia causes alterations in the metabolism of isolated liver slices comparable to those in the intact rabbit. Such alterations in glucose tolerance, response to insulin and power to remove lactic acid from the blood can be studied in these liver slices. Several investigators have thought that the effects of diphtheritic toxemia are caused primarily by damage of the suprarenal by the toxin. If this is true similar results should be obtained with liver slices of rabbits from which the suprarenals have been removed. The authors have compared the effects of complete suprarenalectomy and diphtheritic toxemia on the carbohydrate metabolism of rabbit liver slices and find very wide differences. The results give no support to the view that damage to the suprarenals is important in diphtheritic toxemia.—J. B. Paton.

MCGAVACK, T. H.

Desoxycorticosterone and glucose tolerance in Addison's disease. *Bull. N. Y. Med. Coll., Flower and Fifth Ave. Hosp.* 2: 21. 1940.

Blood glucose levels while fasting and after ingestion

of glucose were routinely lower in cases of Addison's disease whether stabilized with desoxycorticosterone or not, than in control subjects. The failure of desoxycorticosterone to raise blood glucose levels to normal is dependent on an endogenous process rather than on defective alimentary absorption.—H. L. Mason (*Chemical Abstracts*).

RAAB, W.

Roentgen treatment of the adrenal glands in angina pectoris (One hundred cases). *Ann. Int. Med.* 14: 688. 1940.

Roentgen irradiation of the adrenals was employed in an attempt to restrict the discharge of adrenalin in patients with angina pectoris. This was based on the theory that the pain was due to anoxia of the heart muscle resulting from release of adrenalin. Seventy-six out of 100 patients were benefited.—F. A. H.

SOFFER, L. J., F. L. ENGEL AND B. S. OPPENHEIMER.

Treatment of Addison's disease with desoxycorticosterone acetate. *J.A.M.A.* 115: 1860. 1940.

Soffer and his colleagues treated Addison's disease by intramuscular injections and the subcutaneous implantation of pellets of desoxycorticosterone. They present extensive studies on 5 cases, all of whom were benefited by the treatment. The altered blood serum electrolyte pattern was restored to normal. There was no effect on carbohydrate metabolism in 4 cases where dextrose tolerance tests were performed before and after treatment. An overdose of the drug produces a marked rise in blood pressure, and one patient developed severe anginal pains. The authors calculate that when 125 mg. pellets of desoxycorticosterone acetate are implanted, the patient will absorb 0.20 to 0.36 mg. daily. They prefer to give submaintenance doses and supplement treatment by means of oral sodium chloride.—C. P.

THORN, G. W., AND K. EMERSON, JR.

The role of gonadal and adrenal cortical hormones in the production of edema. *Ann. Int. Med.* 14: 757. 1940.

The electrolyte balance of the body appears to be affected significantly by the steroid hormones of the gonads and adrenal cortex. Under certain conditions these hormones may precipitate edema. Restriction of sodium chloride intake combined with potassium medication ameliorates the condition.—F. A. H.

ENDOCRINE GENERAL

BAYER, L. M.

Build variations in adolescent girls. *J. Pediat.* 17: 331. 1940.

A classification of feminine build is described which seeks to sort individuals according to the degree and direction of their secondary sex differentiations. It is based upon a consideration of skeletal proportions and body covering. Two-thirds of a group of adolescent girls fit into categories of hypofeminine (Diana), feminine (Venus), hyperfeminine (Rubens), and virile (Amazon).—M. B. G.

BAYER, L. M.

Weight and menses in adolescent girls, with special reference to build. *J. Pediat.* 17: 345. 1940.

A series of 92 adolescent girls have been studied with regard to certain aspects of weight, menstruation and build. The girls are sorted into build groups designated as hypofeminine (Diana), feminine (Venus), hyperfeminine (Rubens), virile (Amazon) and mixed. The following were noted: 1. Where weight deviations occur, the tendency is toward underweight among the hypofeminines and overweight among the hyperfeminines. 2. The feminines show contrasts with the others in regard to certain aspects of menstruation. In the feminine group, the menarche was reached at a mean of 13.16 years as against a much wider distribution in the other groups. The study gives support to the hypothesis that a relation exists between normal build and normal function. Marked disturbances in weight and menstruation are frequently associated with deviations from normal build.—M. B. G.

CONN, J. W.

The spontaneous hypoglycemias. *J.A.M.A.* 115: 1669. 1940.

Conn classifies the spontaneous hypoglycemias according to their etiologies. Among the organic causes he discusses: *a*) hyperinsulinism, *b*) hepatic disease, *c*) anterior pituitary hypofunction, *d*) adrenal hypofunction, *e*) C.N.S. lesions. He divides functional hypoglycemias into 4 groups, namely: hyperinsulinism, renal glycosuria, severe continuous muscular work, and pregnancy. He gives case histories illustrating the various types of hypoglycemias and discusses the differential diagnosis. The diagnostic procedures and criteria which he has found most useful are: 1, the fasting blood sugar levels, 2, the dextrose tolerance tests, 3, Liver function tests, 4, the clinical course of the patient.—C. P.

GERSTENBERGER, H. J.

Influence of hormonal therapy on the phosphatization of rachitic bones. *Am. J. Dis. Child.* 60: 747. 1940.

The author had previously reported that thyroxin had a healing effect on rachitic metaphyses of light-deficient monkeys. Parathyroid extract had no effect. Rickets may be related to endocrine disturbances. Thyrotropic extracts of the anterior pituitary produced healing of rickets in monkeys which had failed to show any response to prior administration of phosphoric acid solution. Thyrotropic hormone itself is not capable of healing rickets without the administration of phosphoric solution either before or after the former.—M. B. G.

GONADS

ARCHIMEDE, M.

Treatment of the premature with testosterone propionate and with desoxycorticosterone acetate. *Ormoni, Turin* 2: 221. 1940.

Decreased mortality and rapid weight gain were noted in 75 premature infants treated with 1 mg. per day of testosterone propionate or desoxycorticosterone acetate.

Mortality was 3.8% for 51 treated with testosterone and 0% for 24 treated with desoxycorticosterone. Mean increase in body weight per day was 30 to 35 gm., and was greatest in the testosterone treated group. Doses above 1 mg. had no advantage, but proved safe. Treatment was interrupted when body weight reached 2,500 gm.—G. A. E.

CHARNY, C. W.

Testicular biopsy. *J.A.M.A.* 115: 1429. 1940.

The author favors biopsy over aspiration because of the larger sample obtained. The biopsy is performed under procaine infiltration by incising the skin and nicking through the tunicas vaginalis and albuginea with a sharp scalpel. The testis is then pressed until a bead of tubular material extrudes, which is snipped off with a scissors. The author cites 7 case histories illustrating the value of this procedure. The operation has been performed 40 times without mishap, and it has furnished controlled data on therapeutic procedures when performed before and after treatment.—C. P.

DUFFY, P. V., AND J. CORSARO.

Suppression of lactation by testosterone. *J.A.M.A.* 116: 33. 1941.

In a group of 18 postpartum patients where the breasts were engorged, tender and painful, testosterone propionate was given on the 3rd or 4th day postpartum. The dosage was varied from 15 to 75 mg. to determine if possible the minimum therapeutic dose needed. The tenderness and engorgement were relieved dramatically, and lactation was suppressed within 24 to 48 hours. Similar quantities of testosterone were not effective in suppressing lactation in 4 cases in which lactation was definitely established when treatment was begun, and also in 3 cases where testosterone was administered immediately after delivery. Five to ten mg. doses may be used to relieve painful engorgement in nursing mothers. Methyl testosterone orally in doses of 25 mg. at 6-hour intervals produces comparable results to 75 mg. of testosterone propionate subcutaneously.—C. P.

DUNN, C. W.

Stilbestrol-induced gynecomastia in the male. *J.A.M.A.* 115: 2263. 1940.

Dunn reports the case of a ♂ patient, aged 27, treated for a hypersexual state with 480 mg. of stilbestrol over a period of 96 days. The resultant growth of mammary tissue was greater and firmer than that which occurs after estradiol or estriol therapy. Hyposexuality resulted from the treatment.—C. P.

FREED, S. C., E. E. ROSENBAUM AND S. SOSKIN.

Alleged hepatotoxic action of stilbestrol. *J.A.M.A.* 115: 2264. 1940.

Freed and his colleagues treated about 20 menopausal patients with doses of 1 to 10 mg. daily of stilbestrol. They could detect no change in the bromsulfalein retention test of liver function. They conclude that therapeutic doses are not harmful to the human liver.—C. P.

GRAUER, R. C., C. F. BEALL AND G. R. WILSON.

Endometrial response to diethylstilbestrol in radium-induced menopause. *Am. J. Path.* 17: 87. 1941.

The effect of diethylstilbestrol was observed on radium-induced castration and compared with physiological menopause cases and with surgically induced menopause. In cases of bleeding dysfunction curettings were taken prior to radium insertion, and each patient was then exposed to 1,200 to 1,800 mg. hr. of radium. Diagnostic biopsies followed 1 to 2 years after radium insertion, following which 3 mg. stilbestrol was given in daily oral doses for 2 weeks. Biopsies and vaginal smears were taken and were repeated at the end of 5 weeks' treatment. Two weeks were required to produce endometrial proliferation in the physiological cases and 5 weeks in the radium-induced cases. Biopsies after treatment simulated those taken before radium application, showing a highly proliferative non-secretory epithelial response, with stroma cell and myometrial cell proliferation. Bleeding as a result of stilbestrol resulted in 3 of 10 cases, and in 6 of 7 of the physiological cases. It seems probable that radium influence on small blood vessels caused the difference in response. Endometrial and vaginal response to stilbestrol in radium-treated cases is delayed and the dose required is greater than in physiological cases of menopause. There is less tendency to evoke bleeding in radium-treated cases. Radium injures stroma and myometrium, as well as the glands.—From author's abstract.

KREUTZMANN, H. A. R.

Sterility in the male, diagnosis and treatment. *J.A.M.A.* 115: 1424. 1940.

The author states that if urological examination result is negative, then the sterility may be ascribed to some endocrine dysfunction. At present, consistent results are obtained only in those cases where hypothyroidism is the cause. The administration of large doses of testosterone is accompanied by a marked decrease in the number of spermatozoa per cubic centimeter. The normal and abnormal ratios of the sperms were not changed by 5 mg. of testosterone propionate 3 times a week.—C. P.

LIN, H. A-C.

The determination of urinary estrogens in cases of uterine hemorrhage. *Chinese M. J.* 57: 216. 1940.

Determinations in 14 cases of uterine hemorrhage indicated that the urinary output of estrogens is uniformly low in metropathia hemorrhagia.—W. H. Adolph (*Chemical Abstracts*).

QUENTAL, J. B.

On the determination of gonadotropic hormones in the urine of diabetic patients. *Acta med. Rio de Janeiro* 5: 23. 1940.

Gonadotropic hormones in the urine of normal and diabetic patients were studied using the Aschheim-Zondek technic. A pronounced increase was observed in the hormone elimination in all 7 cases studied, values of 50 to 100 M.U. per liter of urine being obtained.—G. G. Villila.

SALMON, U. J., AND S. H. GEIST.

Buccal absorption of α-estradiol in propylene glycol. *Proc. Soc. Exper. Biol. & Med.* 45: 766. 1940.

A method of administering estrogens is described, consisting of the instillation of a solution of α-estradiol in propylene glycol into the sublingual space. Effectiveness of absorption was estimated by the estrogen effect on the vaginal smears and the histologic changes in the vaginal mucosa in a group of 8 estrogen deficient women. The solution contains 0.5 mg. of α-estradiol per cc. of propylene glycol. The patients were given 4 drops, 3 to 6 times daily. Characteristic estrogenic effects were noted, at the end of 1 week, in all patients receiving daily doses of 0.2 and 0.3 mg. of α-estradiol.—U. J. Salmon.

TETTAMENTI, J.

Hormone treatment of adenoma of the prostate. *Rev. medica de Rosario*, No. 2. 1940; *Rev. sud-am. de endocrinol.* 23: 660. 1940.

Testosterone propionate gave relief from difficulties of micturition in 'first grade prostatism.' In incomplete retention no response was obtained. One case of chronic complete retention showed some improvement after administration of 150 mg., but other treatment was employed simultaneously. The subjective feelings were always markedly improved.—A. E. M.

VON HAAM, E., M. A. HAMMEL, T. E. RARDIN AND R. H. SCHOENE.

Clinical studies on stilbestrol. *J.A.M.A.* 115: 2266. 1940.

von Haam et al. conclude from a study of 125 menopausal patients that stilbestrol is a powerful, oral estrogenic substance which is effective in small doses. Treatment had to be discontinued in only 9 cases because of toxic reactions, which varied from nausea and vomiting to dizziness and headaches. One case of psychotic excitement and 2 cases of severe diarrhea occurred. These reactions disappeared as soon as the drug was discontinued. Gastric analyses showed a decreased acid response with nauseating doses of stilbestrol. Excretion of 10–30% of a single ingested dose of 10 to 15 mg. occurred in 10 days. It is suggested that stilbestrol is a valuable drug as long as it is given in small doses over short intervals.—C. P.

WARD, G. G.

Benign gynecologic hemorrhages. *J.A.M.A.* 115: 1625. 1940.

Ward classifies the causes of gynecological hemorrhage as follows: 1, functional, such as endocrine imbalance at puberty, gestational period, and menopause; 2, neoplastic hemorrhages; 3, hemorrhage associated with inflammatory disease; 4, external bleeding associated with pathological gestation; 5, intra-abdominal bleeding as a result of ectopic pregnancy, endometriosis, ruptured ovarian cysts or myomas; 6, miscellaneous causes, such as hemophilia, hypertension. Functional bleeding he further subdivides into the following classes: 1, estrogen excess-progesterone deficiency with a hyperplastic endometrium; 2, hypo- or hyperthyroidism; 3, increased activity of the anterior pituitary. Treatment may consist of progesterone, chorionic-gonadotropin, moccasin snake venom, curettage, intrauterine radium, testosterone propionate, and transfusions when indicated. In a case of post-menopausal bleeding with slightly enlarged uterus and ovaries and hyperplasia of the endometrium, a granulosa cell tumor should be suspected.—C. P.

WIISENBECK, I. A., AND W. P. PLATE.

A case of arrhenoblastoma of the ovary (with hormone investigation). *Nederl. tijdschr. V. geneesk.* 84: 1022. 1940.

A case of arrehenoblastoma in the wall of a cyst is described, containing 3.11 of fluid in which were 170 γ androsterone and 100 γ testosterone with only traces of estrogenic hormones. The tumor contained 6 I.U. of substances stimulating comb growth and 50 U of estrogenic material.—R. Buetner (*Chemical Abstracts*).

YOLTON, N., AND C. REA.

Excretion of androgens and estrogens in males with mammary carcinoma. *Proc. Soc. Exper. Biol. & Med.* 45: 54. 1940.

Men with mammary carcinoma did not differ significantly from the controls in the amounts of androgens and estrogens excreted in the urine.—L. E. Gilson (*Chemical Abstracts*).

ZELSON, C., AND E. STEINITZ.

Treatment of cryptorchidism with chorionic gonadotropic hormone and male sex hormone. *J. Pediat.* 17: 315. 1940.

The authors treated 17 boys with cryptorchidism, two of them with bilateral involvement, by injections of 500 R.U. of chorionic gonadotropic hormone and 5 to 10 mg. of testosterone propionate 3 times a week for a period of 3 to 12 weeks. Complete descent of the testes occurred in 9 (53%) of the boys. These included 4 of 9 boys who had been treated with either hormone alone or successively without any effect. The authors conclude that combined treatment is most effective and advise the following procedure. A course of treatment with chorionic gonadotropic hormone from 300 to 500 R.U. 3 times a week up to a total of 10,000 U should be given. If no response results, a combined course of treatment should then be given after a rest period from one to three months. If no satisfactory result is obtained, the cryptorchidism should be treated surgically. Treatment should be instituted before the boys are 10 years of age.—M. B. G.

HYPOPHYSIS

WILSON, D. M., M. H. POWER AND E. J. KEPLER

Alkalosis and low plasma potassium in a case of Cushing's syndrome: a metabolic study. *J. Clin. Investigation* 19: 701. 1940.

A typical case of Cushing's syndrome was studied because of associated disturbances in plasma electrolytes,

reflected in diminished conc. of K and Cl, increased conc. of HCO_3, elevated pH, and normal conc. of Na and protein, Ca, Mg, P, sulfates. The pattern returned to normal on simultaneous admin. of KCl and NH_4Cl, following which KCl alone maintained a relatively normal pattern. K citrate produced partial correction of abnormal conc. of K, Cl and HCO_3 in plasma. NH_4Cl failed to maintain normal conc. of plasma Cl and HCO_3 after the conc. of plasma K had decreased upon withdrawal of administered K salts. The concs. of other electrolytes in plasma remained essentially normal throughout the period of observation and showed no apparent relation to the metabolic upset. It is suggested the abnormality in distribution of electrolytes resulted from failure of the kidney to retain K and that Cl played only a secondary role as it appears to do in cases of adrenal insufficiency. The therapeutic admin. of KCl did not influence the course of the disease.—From authors' summary.

PANCREAS

Appel, J. W., and J. Hughes.

The effect of large doses of insulin on glucose tolerance. *Am. J. M. Sci.* 199: 829. 1940.

Insulin given over periods as long as 2 months in daily doses large enough to produce coma in patients with normal carbohydrate metabolism resulted in elevation of glucose tolerance curve. This disappeared 2 to 3 months after cessation of insulin administration.—Authors' summary.

Brahn, B.

Insulin suppositories. *Lancet* 238: 829. 1940.

In experiments carried out on rabbits and on healthy human subjects, suppositories consisting of cocoa butter and insulin were used, 1 suppository unit being equal to 10 injection units. The action of the insulin set in soon attaining a maximum in 30 to 40 min., followed by subsidence. In some instances the action in the suppositories was prolonged to as much as 8 hours.—L. B. Shpiner.

Diamond, J. S., S. A. Siegel and J. L. Kantor.

The secretin test in the diagnosis of pancreatic diseases with a report of one hundred thirty tests. *Am. J. Digest. Dis.* 7: 435. 1940.

One hundred and thirty tests on 104 patients were made, 24 normal and 80 pathological, and gave information of disturbed function in chronic states hitherto unrecognized. In cholelithiasis with common duct stones, the pancreas became simultaneously affected. In obstructive lesions with encroachment on pancreatic duct the test gave diagnostic data by virtue of a diminished or absent response. In lues the test seemed to show decreased pancreatic function, as well as in cirrhosis of the liver, chronic alcoholism, acute yellow atrophy and graver forms of toxic hepatitis. In the steatorrheas the test was most valuable in indicating presence of pancreatic deficiency and in differentiating between the idiopathic group including sprue and that with pancreatic lesions. In follow-up studies in the steatorrhea group the test has shown the reversibility of the function and has been consistent with the clinical improvement of the patient, indicating the degree of recovery.—From authors' summary.

Hamilton-Paterson, J. L., and E. E. M. Johnson.

Post-mortem glycolysis. *J. Path. & Bact.* 50: 473. 1940.

Fifty diabetic and non-diabetic cases were studied with reference to the postmortem diagnosis of hyperglycemia and hypoglycemia. Glycolysis takes place rapidly and hypoglycemia cannot be diagnosed unless the blood is examined within 2 hours. Hyperglycemia can be confirmed if a blood sugar of more than 200 is found in the left heart. Glycogenolysis in the liver results in glucose diffusing into the right heart and causing hyperglycemia. In vitro glycosis was studied.—Authors' abstract.

Hart, J. F., and J. R. Lisa.

The rate of occurrence of hypoglycemia. *Endocrinology* 27: 19. 1940.

Routine fasting blood sugar values below 80 mg. are a common finding. A substantial number fall below 70. Blood sugar values may go as low as 28 mg. without shocks. Low blood sugar readings are apparently not associated with any disease or group of diseases. Normal individuals may have occasional low blood sugar values with an otherwise normal blood sugar. Either spontaneous hypoglycemia is not a common condition or routine fasting blood sugars are not reliable guides to its occurrence. —Authors' summary.

Himsworth, H. P.

Insulin deficiency and insulin inefficiency. *Brit. M. J.* 1: 719. 1940.

This is a summary of present knowledge regarding human diabetes mellitus, incorporated in the following statements. There is considerable evidence that two types of diabetes can be differentiated on the basis of the speed with which they react to insulin. In 1 type, the insulin-sensitive type, insulin comes into action rapidly; in the other, the insulin-insensitive type, insulin comes into action slowly. The evidence is compatible with the suggestion that the disease in the sensitive type of case is due to deficiency of insulin, while in the insensitive type the disease is due not to lack of insulin but to impairment of insulin action. At present, although there is evidence that the anterior pituitary gland may be responsible for the diabetes associated with hyperpituitarism, the indictment of the pituitary as a primary factor in ordinary cases of human diabetes mellitus rests purely on analogy.—From authors' summary.

Loew, R. C., L. F. Holland and J. O. Weilbaecher.

The use of crystalline zinc insulin in the treatment of diabetes mellitus. *South. M. J.* 32: 1054. 1939.

Crystalline Zn insulin was tested on 14 selected patients who had not satisfactorily stabilized on other insulins. They responded quickly to the change, becoming aglycosuric at once and remaining so for periods of 2 to 10 months. The total insulin dosage required showed no great change, all but 1 of the 14 requiring 2 injections daily of crystalline Zn insulin, as compared with 3 or 4 in-

jections of regular insulin, alone or combined with regular insulin therapy. The use of crystalline Zn insulin is an advantage to the patient. The ideal insulin, one that is adaptable to all cases, and one in which 1 daily injection would adapt itself to the 24-hour cycle of carbohydrate metabolism, has not yet been developed.—J. G. McAlpine.

MARTIN, H., D. R. DRURY AND S. STROUSE.

Basal insulin requirements in diabetes mellitus. *Arch. Int. Med.* 66: 78. 1940.

In severe diabetes the major problems involve control of the fluctuations of blood sugar following ingestion of food and prevention of hyperglycemia and glycosuria in the postabsorptive state, the latter constituting the basal insulin requirement. To determine whether a basal insulin requirement exists, blood sugar determinations are made when no sugar is present in urine 4 to 6 hours following the evening meal which has been adequately covered by regular insulin and by no PZnI for 24 hours. Diabetic patients with a high renal threshold will require in addition a normal blood sugar content 6 hours following the evening meal. With such requirements fulfilled, a fasting morning blood sugar of 150 mg.% or more indicates the necessity for insulin to cover the basal requirement. The method of determining basal insulin requirement is given, with illustrative case histories, and its therapeutic usefulness is emphasized. PZnI at night is suggested as most suited to cover the basal insulin requirement, while regular insulin is most suited to cover the dietary intake of persons with severe diabetes.—H.O.H.

MATTHEWS, M. W., T. B. MAGATH AND J. BERKSON.

The one hour-two dose dextrose tolerance test, Exton-Rose procedure. Diagnostic significance. *J.A.M.A.* 113. 1531. 1939.

The Exton-Rose glucose tolerance test was used in 117 normal individuals and 304 cases which had been diagnosed as diabetes by other methods and graded according to their severity. The authors found in general that in normal subjects the mean fasting blood sugar was 84.6 mg., in the latent diabetic 94.5 mg. Mean figures of 142 mg. at the half hour and 158 mg. at the hour were found. They concluded a fasting blood sugar of over 120 mg. as diagnostic of diabetes. Blood sugars exceeding 158 mg. at the hour are almost always found only in diabetics. It is believed the specimen obtained 1 hour after injection of dextrose is the most important.—E. A. Baumgartner.

MURLIN, J. R., C. B. F. GIBBS, M. J. ROMANSKY, I. B. STERNHAUSEN AND F. L. TRUAX.

Effectiveness of peroral insulin in human diabetes. *J. Clin. Investigation* 19: 709. 1940.

The influence of hexylresorcinol and a buffering mixture of salts on the intestinal absorption of insulin was tried in 20 patients, with a standard dose set at 100 I.U. pure insulin in solution of 0.125% hexylresorcinol and alkaline salts, at a PH of 10 to 10.5. Up to 8 such doses could be given per day without interfering with digestion. Blood sugar effects of a single dose varied from 0 to 60 mg.% in 45 minutes. The total insulin per 24 hours varied from 200 to 800 I.U. Effects on urine sugar were not proportional to dosage, often being as great after administration of 200 to 300 I.U. as with 600 to 800 I.U. Greatest effects appeared when fasting blood and urinary sugars were high. Equivalent unitage orally in terms of subcutaneous dosage varied from 2.1 to 22 I.U., average less than 10. Results were regarded as only mildly encouraging for the hope of controlling adequately diabetes mellitus by oral insulin.—From *J.A.M.A.* abstracts.

POLATIN, P., H. SPOTNITZ AND B. WIESEL.

Effects of intravenous injection of insulin in treatment of mental disease. *Arch. Neurol. & Psychiat.* 43: 925. 1940.

Twenty-three patients, 19 of whom had psychoses and 4 psychoneuroses, were treated with intravenous injections of insulin over a period of from 2 to 13 weeks to produce rapid hypoglycemia shock with a minimum of coma. With this treatment there was general improvement in physical condition, and 48% revealed some degree of mental improvement. Ten patients with schizophrenia were treated over a period of 2 months or more, and 70% showed some improvement in mental state. None of the patients had convulsions, nor were there any detectable injuries during the course of treatment. The utilization of this method in the treatment of mental disease deserves further investigation.—From authors' abstract.

ROSS, A. T., AND W. W. DICKERSON.

Epilepsy complicated by uncontrollable diabetes mellitus. *Endocrinology* 27: 200. 1940.

Two cases of uncontrollable juvenile diabetes mellitus with epilepsy are presented. Each condition apparently was a separate entity. Convulsions occurred regardless of the diabetic status. Neither hyperglycemia nor ketosis had a consistently significant effect upon the convulsive manifestations. The complexity of attempting to control either or both of the entities is discussed. Such a concurrence is rare.—Authors' summary.

ROVENO, W. S.

The fasting blood sugar curve: a guide for therapy in diabetus mellitus. *J. Lab. & Clin. Med.* 25: 1057. 1940.

A test for gauging the severity of diabetes is described, which consists in making 3 blood sugar estimations at 3-hour intervals on the fasting patient while ambulatory. The resulting curves fall into 3 groups: (1) a continuous descent from the initial reading, all levels being not far above the normal values; (2) a continuous descent from the initial reading, with all levels considerably higher than the normal values and (3) a group of curves, none of which shows a continuous descent, with at least 1 of the last 2 readings being higher than the initial value. In the 1st 2 groups are the persons with mild diabetes that are readily controlled by the diet alone or combined with a single dose of protamine Zn insulin. In the 3rd group are the persons with severe diabetes controlled only with more than 1 dose of insulin. The test appears most useful in the new or untreated patient. By gauging the severity of his disease, a greater degree of efficiency, with economy of time and expense, may be attained in planning therapy.

It is not applicable to patients under treatment since in these it offers only a measure for the adequacy of treatment.—From author's abstract.

SMITH, B., AND W. H. GRISHAW.

Survey of diabetes: statistical data and control comparisons with various insulins. *Arch. Int. Med.* 66: 465. 1940.

A survey of 800 patients with diabetes was made, equally divided into diabetics of acute and of gradual onset. Patients of the former group continue to show an acute response to slight changes in diet or insulin routines. Exaggerated loss of diabetic control would result from mild complications. Slowly acting insulin gave good results in patients with mild diabetes, i.e. requiring 20 U of insulin or less, 1 morning injection of PZnI maintaining complete control. Patients whose condition is in the milder range of moderately severe diabetes requiring 20 to 40 U, were usually unable to maintain good diabetic control on 1 daily injection of the precipitated insulin. Two daily doses of crystalline Zn insulin gave control that was better maintained than that obtained with 2 daily injections of the amorphous insulin. With evenly maintained control improvement is manifested as a lengthening of duration of the effects of insulin, and a number of patients have become listed as mildly diabetic and maintain full diabetic control on a morning dose of crystalline Zn insulin alone. Selection of an insulin routine for patients with severe acute diabetes (requiring 40 or more U) often requires a period of strict observation. PZnI alone is not adequate, nor is 1 daily injection. When taken twice daily, there may result periods of shock, with the extreme and erratic symptoms peculiar to the persisting hypoglycemia from PZnI, apparently the result of its prolonged effect. Most satisfactory results have been obtained by a morning dose of crystalline Zn insulin together with PZnI at night.—H.O.H.

SPIEGELMAN, ANNA R.

Influence of estrogen on the insulin requirement of the diabetic. *Am. J. M. Sc.* 200: 228. 1940.

The administration of 10,000 I.U. of estrogenic hormone twice a week to a series of 9 diabetic women was associated with a diminution in their insulin requirement. The average daily insulin requirement did not return to the pre-estrogenic level even after estrogen had been discontinued for a period of 3 months. In the premenopausal group the diminution in the insulin requirement associated with the administration of estrogen was greater and more sustained than in the postmenopausal group.—Author's abstract.

STADIE, W. C.

Fat metabolism in diabetes mellitus. *J. Clin. Investigation* 19: 843. 1940.

The problem of fat metabolism in diabetes mellitus and its relation to ketonuria is reviewed and discussed. Evidence favoring the replacement of the successive beta oxidation hypothesis of fatty acids by the multiple alternate oxidation hypothesis is presented. It is shown that the diabetic animal utilizes ketone bodies in the periphery abundantly and independently of carbohydrate oxidation. The hypothesis of obligatory coupling of ketone body-carbohydrate oxidation in diabetes mellitus is not supported by the quantitative data in a series of cases. A simple hypothesis of fat metabolism in diabetes mellitus is presented and shown to conform to the observations in these cases.—Author's summary.

TOLSTOI, E., AND F. C. WEBER, JR.

Protamine zinc insulin: a clinical study. *Arch. Int. Med.* 66: 670. 1940.

Eighty-four patients with diabetes mellitus were treated with 1 dose daily of PZnI. No particular effort was made to maintain the urine free from sugar, and yet only 27 patients revealed amost continuous glycosuria throughout the period of study, one year. Results, presented, in detail, show the great majority maintained weight and many gained. None presented any symptoms of diabetes mellitus and only 1 revealed, rarely, mild acetonuria. Diets were not weighed. Incidence of infections was no greater than in other patients. Guiding principles in maintaining a state of carbohydrate utilization are based on maintenance of weight, freedom from symptoms and absence of ketone bodies in urine.—From authors' summary.

WALLACE, D. H.

Prognosis in diabetes in childhood. *Glasgow M. J.* 16: 1. 1940.

Analyses of results are reported, obtained 77 from cases since 1924. Seventy were followed up. Eighteen died, 4 in coma associated with some infection, 2 of uncomplicated infection, 11 in coma with no other cause and 1 from prematurity and atresia of the pancreas. Average duration of life in the 18 cases was 2.3 years. Majority of deaths occurred within 2 years from onset of disease. Prognosis improves after survival longer than 2 years. The average duration of the disease in the 52 patients who are still alive has been 4.14 years. In these tolerance has improved in 17, has diminished in 26, and is stationary in 9.—From *J.A.M.A.* abstracts.

WATSON, E. M.

The comparative efficacy of various methods for administering insulin. *Canad. M.A.J.* 41: 444. 1940.

Observations on 40 diabetics showed that in order to gain the individual physiological effects of regular insulin and of PZnI, these must be administered separately. When mixed, the regular insulin is converted apparently into protamin insulin, and only the delayed action on blood sugar, characteristic of the latter, is obtained. Many diabetic patients can be treated best by the judicious concurrent use of the 2 types of insulin.—Author's summary.

WAUCHOPE, G. M.

Zinc protamine insulin and soluble insulin. Interaction in combined doses. *Lancet* 238: 962. 1940.

Blood sugar curves were estimated on 2 different days in 17 9 patients, hospitalized and on a balanced diet. On the first day PZnI and SI were given in the same syringe as usual, and on the 2nd day were given sepa-

rately. When the 2 were given together the action of SI was either delayed or prevented entirely. In all cases a larger proportion of SI was needed when given in the same syringe with PZnI to produce a hypoglycemic response. It would appear to be more economical and to ensure more accurate balancing to give PZnI and SI separately, or at least the two should not be allowed to mix.—L. B. Shpiner.

WILDER, R. M.

Clinical diabetes mellitus and hyperinsulinism. xvii +459 pp. W. B. Saunders Co. Phila., 1940. $6.00.

The experiences of the author and of his colleague are detailed in relation to the subjects announced in the title. Twenty-two chapters are devoted to diabetes and 4 (57 pages) to hyperinsulinism. Some of the component chapters are modifications of lectures given by the author or his associates; some of them, at least in part, have been printed before, but the monograph does not suffer from this fact. It gives a well-balanced, concise, and critical survey of diabetes in both its theoretical and practical aspects. It is of value not only for the clinician interested in diabetes but also for the research worker who desires to acquaint himself with many interesting and pertinent facts. References are given at the end of each chapter. There is an appendix containing useful information on foodstuffs and pertinent biometrical material. The bibliography and subject indices together cover 40 pages.—A. Goudsmit, Jr.

PARATHYROIDS

ANONYMOUS.

A new conception of parathyroid function. *Brit. M. J.* 2: 59. 1940.

This contains rather unfavorable comment concerning the theory of parathyroid function suggested by Helfet, on the basis that even as a preliminary report the conclusions were unjustified and the recommended clinical treatment unsafe since it was based on theory rather than on experience. According to the critic, it has been recognized for some time that the parathyroids mobilize Ca from the bones and stimulate excretion of phosphate by the kidneys. Helfet assumed the parathyroid exerts its primary effect on P metabolism, and suggested that in generalized fibrosa cystica, rheumatoid arthritis and Paget's disease there is a relative hyperparathyroidism. When the body is unable to cope with the phosphates their accumulation in the blood is a stimulus to increased parathyroid activity. Diminution of phosphate absorption was advised, and administration of aluminum acetate was recommended, the latter to combine with phosphate in the intestine, precipitating aluminum phosphate which is excreted unchanged.—J. B. Paton.

ANONYMOUS.

Phosphate intake and the parathyroids. *Lancet* 239: 141. 1940.

In a review of Helfet's recent paper a more favorable estimate of his work is given than appeared in the *Brit. M. J.* (4149) 1940. The reviewer believes Helfet has opened a promising approach to this obscure subject.—J. B. Paton.

BOWERS, R. F.

Hyperparathyroidism. *New Internat. Clin.* 3: 277. 1940.

The incidence and diagnosis of hyperparathyroidism are discussed. Demineralization of bones, muscular weakness, joint pains of the arthritic type and renal calculi are the usual manifestations of dysfunction of the parathyroids. A case with these symptoms is reported in which an adenoma of the parathyroid was removed with excellent results. Two years after operation the patient, who had been bedridden before operation, was improved and able to lead an active life; the demineralization of the bones, however, was no less in x-rays at this time than in those taken before operation.—Author's abstract.

CURTIS, J. K.

Parathyroid insufficiency treated with dihydrotachysterol. *M. Clin. N. A.* 24: 833. 1940.

In parathyroid insufficiency, whether postoperative or idiopathic, therapy is directed at raising blood Ca level, which may be carried out in a number of ways. The immediate treatment is intravenous Ca, usually in the form of 10% Ca gluconate, 10 to 20 cc. administered slowly. The treatment of chronic parathyroid insufficiency has, however, been discouraging until the introduction of dihydrotachysterol (A.T. 10). Chemically A.T. 10 (Antirachitic preparation No. 10) is a derivative of irradiated ergosterin. It increases the Ca absorption from the intestine and the excretion of phosphorus in the urine. The action of A.T. 10 is more rapid than that of vitamin D and more prolonged than that of parathormone but is not so prompt as the latter in raising blood Ca. The dosage varies. Its action is cumulative and prolonged. Ten cc. daily may be given for a week or two and, with symptomatic improvement, the dose is diminished. The usual maintenance dose is 1 cc. daily. It is important to make frequent blood Ca determinations.—From author's abstract.

GARRAHAN, J. P., AND G. F. THOMAS.

Calcium fractions in infantile spasmophilia. *Am. J. Dis. Child.* 60: 249. 1940.

Six cases of infantile spasmophilia were studied, with determinations of blood and spinal fluid Ca. Bibliographic data on Ca fractions, value of spinal fluid Ca as representing the diffusible Ca of the blood, and on quantitative changes of the same in infantile spasmophilia are reviewed, with effects on fractions and the response to administration of parathyroid extract in healthy and sick children In infants affected with spasmophilia the Ca of spinal fluid does not show marked quantitative changes.—From authors' summary.